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14. ABSTRACT

Individuals with germline mutations in *BRCA1* have an elevated but incomplete risk of developing ovarian cancer suggesting the presence of genetic modifiers of ovarian cancer in this population. A genome wide association study (GWAS) for ovarian cancer in BRCA1 mutation carriers has identified several novel modifiers of ovarian cancer risk for BRCA1 mutation carriers that can be used for individualized ovarian cancer risk assessment.

15. SUBJECT TERMS
BRCA1, ovarian cancer, genome-wide association study, association study

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1. Introduction:

Inactivating mutations in the *BRCA1* tumor suppressor gene have been detected in approximately 10% of all ovarian cancers. Individuals with germline mutations in *BRCA1* have a substantially increased risk of developing ovarian cancer as compared to the general population, with an estimated cumulative risk of ovarian cancer by age 70 of 39% [1]. These findings indicate that although *BRCA1* mutation carriers are at high risk for developing ovarian cancer, a sizeable proportion of women who carry a deleterious mutation will not develop this disease. In addition, the findings show that there is considerable variation in the age of onset of ovarian cancer in this population. This variable penetrance and age of onset of ovarian cancer suggest that there are additional genetic and environmental factors that modify the age specific risk of ovarian cancer for *BRCA1* mutation carriers [2]. Common genetic variants that are associated with the risk of ovarian cancer have recently been identified through candidate gene and genome wide association studies in the general population [3,4]. This suggested that common genetic variants may also modify ovarian cancer risk in carriers of *BRCA1* mutations. Identification of these genetic risk factors may prove useful for identifying those *BRCA1* carriers at elevated or lowered risk of ovarian cancer compared to the average *BRCA1* carrier. Women at increased risk may subsequently benefit from enhanced screening or certain prevention measures such as prophylactic oophorectomy, whereas women at lowered risk may be able to avoid these types of intervention. Thus, we proposed a study aimed at identifying genetic risk factors for ovarian cancer in *BRCA1* mutation carriers through a genome wide association study in *BRCA1* mutation carriers. The overall intent was to complete a genome wide association study of *BRCA1* carriers, validate candidate risk modifiers, assess the contribution of these modifiers to sporadic ovarian cancer, and develop risk prediction models for BRCA1 mutation carriers that incorporate the common genentic modifiers identified in the GWAS.

2. Key Words:

BRCA1, ovarian cancer, genome-wide association study, risk factors

3. Overall Project Summary:

Aim 1: To conduct a genome-wide association scan in 1,000 *BRCA1* carriers with ovarian cancer and 1,000 age-matched unaffected *BRCA1* carriers.

Task 1. Aliquot DNA samples for genotyping.

All samples used for the GWAS were contributed by collaborators in the Consortium of Investigators of Modifiers of *BRCA1*/2 (CIMBA) [5]. We collected DNA samples in the Couch laboratory in two phases. The first phase included DNA from 361 BRCA1 mutation carriers diagnosed with ovarian cancer and 1250 unaffected BRCA1 carriers. The second phase resulted in collection of DNA from an additional 434 *BRCA1* mutation carriers diagnosed with ovarian cancer [3].

Task 2. Genotype DNA samples on Human 660W-Quad arrays.

We genotyped allof these DNA samples on on Human660W-Quad arrays in the Medical

Genome Facility at the Mayo Clinic. In addition we acquired GWAS genotype data for 120 additional *BRCA1* mutation carriers affected with ovarian cancer from CIMBA collaborators, resulting in GWAS genotype data from 915 *BRCA1* ovarian cancer cases [3].

Task 3. Genotype quality control analysis.

Genotyping calls were obtained using the standard Illumina calling algorithm incorporated in the BeadStudio software. As expected gender checks using PLINK software failed to identify male *BRCA1* carriers. Duplicates were identified by identify-by-descent analyses and were removed. Quality control thresholds of >95% variant call rates and >95% sample call rates were applied. Variant with minor allele frequency <0.05 were excluded. In addition single nucleotide polymorphisms (SNPs) displayed divergence from Hardy Weinberg equilibrium p<1 x 10-7 were removed. Final analyses included 897 BRCA1 mutation carriers with ovarian cancer and approximately 540,000 SNPs. Genetic relatedness among samples from different countries and ethnicities can introduce heterogeneity into association studies and cause important SNPs to be overlooked. While this study was restricted to Caucasian BRCA1 carriers the study did include DNA samples from many countries. To account for population stratification, the genotyping data in combination with HapMap data (CEU, Yoruban, Han Chinese populations) on 40,000 SNPs with known phase were analyzed by Eigenstrat. A total of 17 individuals were excluded because of non-caucasian admixture of between 15% and 25% [3].

Task 4. Data analysis.

Final analyses of genotyping data included 897 *BRCA1* mutation carriers with ovarian cancer and approximately 540,000 single nucleotide polymorphisms (SNPs). In collaboration with Drs. Douglas Easton and Antonis Antoniou at the University of Cambridge, we evaluated associations with both breast and ovarian cancer using a retrospective likelihood model. This accounts for the age extremes of affected and unaffected and also applies age related penetrance estimates for *BRCA1* carriers. Carriers were censored at age of onset of disease for those affected with breast or ovarian cancer and age of last follow up or age at prophylactic mastectomy/oophorectomy for those with no cancer diagnosis. Analyses were adjusted for Country of origin because samples from 26 different centers in 18 countries were included in the study.

For ovarian cancer, no SNPs showed genome wide significance (p<1 x 10-7). However, 10 SNPs exhibited associations of $p<1x10^{-5}$ and 37 had associations of $p<1x10^{-4}$. Interestingly, rs1339552 on chromosome 9 in *BCN2* and rs7651446 from *TIPARP* on chromosome 3 that exhibited genome wide associations with ovarian cancer in the general population also showed highly significant associations ($p=1.9x10^{-5}$ and $p=1.7x10^{-4}$, respectively) with ovarian cancer in *BRCA1* mutation carriers [3]. These loci can be considered genetic risk factors for ovarian cancer in *BRCA1* mutation carriers.

Aim 2: To further evaluate observed associations between ovarian cancer risk and SNPs implicated in Aim 1 by genotyping 1,500 *BRCA1* ovarian cancer cases and 1,500 unaffected *BRCA1* carriers.

Task 5. Design and order 384 arrays.

Phase 1: Validation of Chromosome 19p13.1 associations
An interim validation study of the 89 SNPs most significantly associated with breast cancer in the BRCA1 GWAS was undertaken. SNPs were selected based on p-values identified in Task 4, and a multiplex Illumina bead array was designed.

Phase 2: GWAS validation studies
We planned to evaluate the 384 most significantly associated SNPs from the *BRCA1* ovarian cancer GWAS in 3,000 additional *BRCA1* mutation carriers including 1,500 with ovarian cancer. Instead in 2010 we designed a SNP array (iCOGS) containing 211,000 candidate SNPs from GWAS of various tumor types. A total of 35,000 candidate SNPs were selected from the *BRCA1* GWAS including 6,000 from the *BRCA1* Ovarian Cancer GWAS.

Task 6. Aliquot DNA samples for replication study.

Phase 1: Validation of Chromosome 19p13.1 associations
An additional 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers, which included 1,465 *BRCA1* mutation carriers and 453 *BRCA2* mutation carriers with ovarian cancer were collected from CIMBA members. Each of these samples was evaluated for DNA quality by conducting picogreen and E-gel (Invitrogen) analysis. Samples with low levels of DNA (<250ng available) or with degraded DNA, identified as smearing on Egel analysis, were excluded. Samples were manually aliquoted into 96-well plates in preparation for genotyping.

Phase 2: GWAS validation studies
We proposed to genotype 14,000 DNA samples from BRCA1 mutation carriers on these arrays in contrast to the 3,000 originally planned for Stage 2 of the ovarian cancer GWAS. Investigators in 52 CIMBA groups from around the world provided non-amplified genomic DNA samples from approximately 15,000 from female *BRCA1* mutation carriers including 1,400 with ovarian cancer. Each of these samples was evaluated for DNA quality by conducting picogreen and E-gel (Invitrogen) analysis. Samples with low levels of DNA (<250ng available) or with degraded DNA, identified as smearing on Egel analysis, were excluded (n=1,200). A total of 12,700 Caucasian, 150 Malaysian and 204 Hong Kong DNA samples were identified as useful for further validation studies. Overall, high quality DNA samples from 8,054 unaffected and 1,264 *BRCA1* carriers affected with ovarian cancer were available for genotyping. Samples were manually aliquoted into 96-well plates in preparation for genotyping.

Task 7. Genotype 3,000 DNA samples using the 384 SNP array.

Phase 1: Validation of Chromosome 19p13.1 associations
An additional 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers including 1,465 *BRCA1* mutation carriers and 453 *BRCA2* mutation carriers with ovarian cancer were genotyped for 89 candidate SNPs on an Illumina custom bead array in the Medical Genome Facility at the Mayo Clinic.

Phase 2: GWAS validation studies
Genotyping of 8,054 unaffected and 1,264 *BRCA1* carriers affected with ovarian cancer using the

iCOGS array was performed in the Medical Genome Facility at the Mayo Clinic.

Task 8. Genotype quality control analysis.

Phase 1: Validation of Chromosome 19p13.1 associations
Quality control was performed as described for Task 3. Seven SNPs displayed SNP call rates of <95% and were excluded.

Phase 2: GWAS validation studies
Quality control was performed as described for Task 3. Testing of the iCOGS array showed that 204,000 of the SNPs yielded good quality genotyping. The other 7,000 SNPs were excluded from further consideration.

Task 9. Data analysis.

Phase 1: Validation of Chromosome 19p13.1 associations
Association studies for breast cancer among BRCA1 mutation carriers identified genome wide significant associations for five SNPs from a single locus on chromosome 19p13.1 *(P*= $2.3x10^{-9}$ to $3.9x10^{-7}$). To assess the influence of these SNPs on ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers we used a competing risk analysis that accounted for the effects on breast and ovarian cancer in parallel. In this competing risk analysis rs67397200 at 19p13.1 was strongly associated with ovarian cancer risk in *BRCA1* (HR=1.16; 95%CI 1.05-1.29; p=3.8x10-4) and *BRCA2* (HR=1.30; 95%CI 1.10-1.52; p=1.8x10-3) mutation carriers. Similar results were obtained for rs8170 at 19p13.1. These results suggested that variants in this locus were modifiers of ovarian cancer risk among *BRCA1* and *BRCA2* mutation carriers [6]. This was the first study to the identify common variants that influenced both breast and ovarian cancer risk in either *BRCA1* or *BRCA2* mutation carriers [6].

Phase 2: GWAS validation studies
Analyses of associations with ovarian cancer risk for 8,054 unaffected and 1,264 affected *BRCA1* carriers (Stage 2) revealed no evidence of inflation in the association test-statistic (λ=1.039, adjusted to 1000/1000 cases/controls λ=1.018). When combining the iCOGS and original GWAS, genotype data from 9866 unaffected *BRCA1* mutation carriers and 1839 affected with ovarian cancer were available for analysis. A total of 62 SNPs in 17 regions were associated with ovarian cancer risk for *BRCA1* carriers at $P<10^{-4}$. Associations (P<0.01) with ovarian cancer risk were observed for SNPs in all known ovarian cancer susceptibility loci from the general population (3q25, 8q24, 9p22, 17q21, 19p13) except 2q31. After excluding SNPs from known ovarian cancer susceptibility regions, there were 48 SNPs in 15 regions with $P=5\times10^{-7}$ to 10^{-4}. Genotype data for 5 SNPs from four of these loci were available from 2,204 *BRCA1* unaffected carriers and 442 *BRCA1* carriers (stage 3). In the combined stage 1-3 analyses, SNPs rs17631303 and rs183211 (r^2=0.68) on chromosome 17q21.31 had genome wide significant associations for ovarian cancer, of 2.8×10^{-10} and 2.0×10^{-9}, respectively. The SNP rs4691139 at 4q32.3 also had a genome wide significant association ($p=3.4\times10^{-8}$). None of these SNPs were associated with breast cancer in *BRCA1* mutation carriers [7].

Imputation using data from the 1000 Genomes Project, identified several SNPs in 17q21.31 with stronger associations than the most significant genotyped SNP in the combined *BRCA1/2* analysis (rs169201, $P=6.24\times10^{-11}$) [7]. This large region of strong linkage disequilibrium has previously been identified as a 17q21.31 inversion (~900kb long) consisting of two haplotypes (termed H1 and H2). The most significant SNP (rs140338099 (17-44034340), $P=3\times10^{-12}$) located in *MAPT*, was highly correlated ($r^2=0.78$) with the most significantly associated genotyped SNP (rs169201) in *NSF*. This locus appears to be distinct from a previously identified sporadic ovarian cancer susceptibility locus located >1Mb distal on 17q21 (spanning 43.3-44.3Mb, build 36.3) [4]. None of the SNPs in the novel region were strongly correlated with any of the SNPs in the 43.3-44.3Mb region (maximum r2 =0.07). The most significantly associated SNP from the *BRCA1* GWAS from the 43.3-44.3Mb locus was rs11651753 (p=4.6•10-4) (r2<0.023 with the seven most significant SNPs in the novel 17q21.31 region). An analysis of the joint associations of rs11651753 and rs17631303 from the two 17q21 loci with ovarian cancer risk for *BRCA1* carriers (Stage 1 and 2 samples) revealed that both SNPs remained significant in the model (P-for inclusion=0.001 for rs11651753, 1.2x10-6 for rs17631303), further suggesting that the two regions are independently associated with ovarian cancer for *BRCA1* carriers.

The minor allele of rs4691139 at the novel 4q32.3 region was also associated with an increased ovarian cancer risk for *BRCA1* carriers (per-allele HR=1.20, 95%CI:1.17-1.38), but was not associated with breast cancer risk [7]. Analysis of associations with variants identified through 1000 Genomes Project based imputation of the Stage 1 and 2 samples, also revealed 19 SNPs with stronger evidence of association ($P=5.4\times10^{-7}$ to 1.1×10^{-6}) than rs4691139 on 4q32.3. All were highly correlated (pairwise $r^2>0.89$) and the most significant (rs4588418) had $r^2=0.97$ with rs4691139 [7]. No association was found between rs4691139 and ovarian cancer risk in the general population based on data by the Ovarian Cancer Association Consortium (OCAC) in 18,174 cases and 26,134 controls (Odds Ratio=1.00, 95%CI:0.97-1.04, P=0.76). Thus, the 4q32.3 is an ovarian cancer risk factor specific to *BRCA1* mutation carriers.

Table 2. Associations with breast and ovarian cancer risk for SNPs found to be associated with risk at all 3 stages of the experiment. [7]

SNP, Chr, Position, Allele1/Allele2	Stage	Number Unaffected	Affected	Hazard ratio (95%CI)	P-trend
rs17631303, 17q21, 40872185, A/G	Stage 1	1797	574	1.46 (1.22–1.74)	1.3×10−5
	Stage 2	7996	1257	1.20 (1.07–1.35)	1.5×10−3
	Stages1+2	9793	1831	1.27 (1.16–1.40)	3.0×10−7
	Stage 3	2204	442	1.27 (1.07–1.51)	0.014
	Combined	11997	2273	1.27 (1.17–1.38)	1.4×10−8
rs183211, 17q21, 42143493, G/A	Stage 1	1812	575	1.45 (1.23–1.71)	2.5×10−5
	Stage 2	8054	1264	1.20 (1.07–1.33)	1.1×10−3
	Stages1+2	9866	1839	1.25 (1.15–1.37)	5.7×10−7
	Stage 3	2204	442	1.25 (1.06–1.48)	0.018
	Combined	12070	2281	1.25 (1.16–1.35)	3.1×10−8
rs4691139, 4q32.3, 166128171, A/G	Stage 1	1812	575	1.24 (1.08–1.42)	3.6×10−3
	Stage 2	8054	1264	1.18 (1.08–1.29)	1.3×10−4
	Stages1+2	9866	1839	1.20 (1.11–1.29)	1.1×10−6
	Stage 3	2204	441	1.20 (1.04–1.39)	9×10−3
	Combined	12070	2280	1.20 (1.17–1.38)	3.4×10−8

In summary, SNPs in 3q25, 4q32.3, 8q24, 9p22, 17q21.31, and 19p13 were associated with ovarian cancer in BRCA1 mutation carriers.

Note: There are many publications resulting from this grant beyond those referenced in this report (see Publications, Abstracts, and Presentations). Funding from the grant was used to design the iCOGS and Oncoarray custom genotyping arrays, and was used to cover the cost of genotyping BRCA1 carrier DNA samples for the GWAS, iCOGS, and Oncoarray projects. Any manuscript using these arrays or using data derived from genotyping studies of BRCA1 carriers using these arrays was required to acknowledge the grant.

Aim 3: To evaluate risk modifiers from the *BRCA1* breast cancer GWAS and risk factors from sporadic ovarian cancer GWAS as modifiers of ovarian cancer in *BRCA1* carriers.

Task 10. Compare data with *BRCA1* breast GWAS and sporadic ovarian GWAS.

Meta-analysis for ovarian cancer risk in BRCA1 carriers and the general population

To improve statistical power to identify ovarian cancer risk loci for *BRCA1* mutation carriers, a meta-analysis of association test results from the *BRCA1* iCOGS study (12,790 unaffected; 2,462 affected) and Ovarian Cancer Association Consortium iCOGS study of ovarian cancer in the general population (18,174 EOC cases; 26,134 controls) was conducted. Six new genome wide significant loci were identified through this process including: rs3820282 in *WNT4* ($p=2.0 \times 10^{-8}$); rs12039431 *RSPO1* ($p=1.44 \times 10^{-11}$); rs17329882 in *SYNPO2* ($p=1.95 \times 10^{-8}$); rs115344852 in *GPX5* ($p=3.15 \times 10^{-8}$); 136138765 in *ABO* ($p=1.95 \times 10^{-8}$); rs8044477 in GOT2 ($p=1.0 \times 10^{-8}$). All were novel associations that also showed significance ($p<0.05$) in *BRCA1* carriers alone. This effort increased the number of risk loci for ovarian cancer in *BRCA1* mutation carriers to 18 [8]. All of these ovarian cancer risk loci combined explain 3.9% of the excess familial relative risk of epithelial ovarian cancer in the general population and account for approximately 5.2% of the polygenic modifying variance for epithelial ovarian cancer in *BRCA1* mutation carriers and 9.3% of the variance in *BRCA2* mutation carriers.

Ovarian cancer risk models

All variants associated with ovarian cancer risk in *BRCA1* carriers were used to develop risk models for improved age specific ovarian cancer risk assessments for *BRCA1* mutation carriers. Based on the distribution of the established *BRCA1* ovarian cancer risk modifiers, the 5% of *BRCA1* mutation carriers at lowest risk will have a lifetime risk of developing ovarian cancer of 28% or lower whereas the 5% at highest risk will have a lifetime risk of 63% or higher. Such differences in lifetime or age-specific risks may have practical implications for cancer screening, timing of interventions and family planning for *BRCA1* mutation carriers [7,8].

Position Dependent Risks associated with *BRCA1* and *BRCA2* mutations

An observational study of women with disease-associated *BRCA1* or *BRCA2* mutations who were ascertained between 1937 and 2011 (median, 1999) was conducted. The international sample comprised 19,581 carriers of *BRCA1* mutations and 11,900 carriers of *BRCA2* mutations from 55 centers in 33 countries on 6 continents. Among *BRCA1* mutation carriers, 9052 women (46%) were diagnosed with breast cancer, 2317 (12%) with ovarian cancer, 1041 (5%) with breast and ovarian cancer, and 7171 (37%) without cancer. Among *BRCA2* mutation carriers, 6180 women (52%) were diagnosed with breast cancer, 682 (6%) with ovarian cancer, 272 (2%) with breast and ovarian cancer, and 4766 (40%) without cancer. Hazard ratios for breast and

ovarian cancer were estimated based on mutation type, function, and nucleotide position. The ratio of breast vs ovarian cancer hazard ratios (RHR) was also estimated.

In *BRCA1*, an ovarian cancer cluster region (OCCR) from c.1380 to c.4062 (approximately exon 11) ($P = 9 \times 10^{-17}$) was identified. In *BRCA2*, two OCCRs were identified. The first (OCCR1) spanned c.3249 to c.5681 ($P = 6 \times 10^{-17}$). The second OCCR spanned c.6645 to c.7471 ($P = 0.001$) [9]. In summary, breast and ovarian cancer risks varied by type and location of *BRCA1/2* mutations. With appropriate validation, these data may have implications for risk assessment and cancer prevention decision making for carriers of BRCA1 and BRCA2 mutations [9].

19p13.1 fine mapping

We previously reported that variants from the 19p13.1 locus were associated with ovarian cancer risk with the rs67397200 SNP at 19p13.1 associated with ovarian cancer risk in *BRCA1* (HR=1.16; 95%CI 1.05-1.29; $p=3.8x10^{-4}$) and *BRCA2* (HR=1.30; 95%CI 1.10-1.52; $p=1.8x10^{-3}$) mutation carriers. This SNP and others in this locus were also associated with breast cancer risk in *BRCA1* mutation carriers. To fine map the 19p13.1 locus in an effort to identify the causative variants in this region a meta-analysis of results from the OCAC and *BRCA1* ovarian cancer studies and the BCAC and *BRCA1* breast cancer studies using 1000 Genomes imputed SNP was conducted. Genotyping data from the iCOGS genotyping array for 438 SNPs in this region in 46,451 breast and 15,438 ovarian cancer cases, 15,252 *BRCA1* mutation carriers and 73,444 controls were used. A region containing 13 highly correlated SNPs spanning the *BABAM1*, *ANKLE1* and *ABHD8* genes was associated with serous ovarian cancer (top hit rs4808075, $P=9.2x10^{-20}$), ER-negative breast cancer (rs67397200, $P=1.1x10^{-13}$) and breast cancer in *BRCA1* mutation carriers (rs61494113, $P=7.7x10^{-16}$). This region was also associated specifically with triple negative breast cancer in the general population (P-diff=$2x10^{-5}$). Functional characterization of this locus was performed in breast and ovarian tissues and cell lines. Genotype-gene expression associations were identified for *ANKLE1* in normal ovarian epithelial cells (P=0.002) and for *ABHD8* in breast and ovarian tumors ($P = 3.0x10^{-5}$) and normal breast tissues ($P=2x10^{-3}$); *ABHD8* overexpression induced a significant reduction in invasion and migration; chromosome conformation capture (3C) identified an interaction between four risk SNPs and the *ABHD8* promoter*;* CRISPR/Cas9 targeted deletion of a risk SNP (rs56069439) overlapping a putative enhancer induced *ANKLE1* downregulation; and mRNA stability and enhancer assays indicated functional effects for six candidate causal SNPs. Taken together, these data suggest that multiple risk SNPs in this region regulate *ABHD8* and *ANKLE1* expression, and indicate there are common underlying mechanisms in both breast and ovarian cancer.

Task 11. Design genotyping assays for candidate SNPs.

We designed a custom Illumina array named the 'OncoArray', in order to replicate previous GWAS findings and identify new cancer susceptibility loci. The OncoArray includes ~533,000 variants (of which 260,660 formed a GWAS backbone) and has been used to genotype over 500,000 samples, including ovarian cancer case-control studies of the Ovarian Cancer Association Consortium (OCAC) and *BRCA1* and *BRCA2* mutation carriers of the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA).

Task 12. Genotype *BRCA1* carrier DNAs for candidate SNPs.

A total of 15,694 *BRCA1* mutation-carriers including 2,372 with ovarian cancer and 10,988 *BRCA2* mutation carriers including 849 with ovarian cancer were genotyped on the Oncoarray in the Mayo Clinic, NCI-supported Center for Inherited Disease Research, Genome Quebec, and the University of Cambridge. Oncoarray sample quality control was essentially as described for Task 3. Samples with genotyping call rate < 95%, excessively low or high heterozygosity, not female, ambiguous sex, or duplicates (cryptic or intended) were excluded. SNPs with a call rate <95%, SNPs deviating from Hardy-Weinberg equilibrium ($P<10^{-7}$ in controls or unrelated samples in CIMBA and $P<10^{-12}$ in cases) and SNPs with concordance <98% among 5,280 duplicate pairs were excluded. For the imputation, SNPs with a MAF<1%, call rate <98%, or not linked to the 1000 genomes reference were excluded. Of the 533,631 SNPs manufactured on the array, 494,813 SNPs passed the initial quality control and 470,825 SNPs were used for imputation.

Task 13. Data analysis.

At the conclusion of the grant the research described below had not yet been completed. We include a brief description of the data analysis and outcome from the Oncoarray project that has been completed since then in order to demonstrate that all Tasks in the SOW were completed. Much of this material is unpublished.

To identify SNPs associated with ovarian cancer data from OCAC and CIMBA from iCOGS and Oncoarray studies were combined in a meta-analysis. We obtained genotype data on 3,342 (584 affected) *BRCA1* and 1,424 (105 affected) *BRCA2* non-overlapping samples from iCOGS array. When combined with the oncoarray study, genotype data from 19,036 *BRCA1* carriers including 2,933 with ovarian cancer and 12,412 *BRCA2* mutation carriers including 954 with ovarian cancer were available for analysis. The OCAC OncoArray data set comprised 63 genotyping project/case-controls sets including 66,450 samples from seven genotyping projects: 40,941 controls, 22,406 invasive cases and 3,103 borderline cases. For the logarithm of the per-allele hazard ratio estimate for the association with ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers and the logarithm of the per-allele odds ratio estimate for the association with ovarian cancer in OCAC. Association analyses for OCAC revealed 12 novel loci associated with ovarian cancer at genome-wide significance ($p<5x10^{-8}$) in the general population (unpublished data). The meta-analysis of OCAC and CIMBA revealed three additional ovarain cancer loci. Eighteen of the 22 previously published ovarian cancer loci were associated with the same histotype at genome-wide significance. Of these, 11 showed an association with serous ovarian cancer risk for *BRCA1* mutation carriers and eight showed an association with risk for *BRCA2* carriers (P<0.05) (unpublished data). In total there are 34 loci associated with various subtypes of ovarian cancer for women of European ancestry, of which 27 are associated with all invasive serous ovarian cancer (P<0.01) and 27 are associated with ovarian cancer in BRCA1 mutation carriers. These 27 loci account for approximately 6.4% of the polygenic risk in the population (unpublished data). Incorporating common susceptibility variants into risk assessment tools will improve risk prediction and may be particularly useful for refining risk estimates in *BRCA1* and *BRCA2* mutation carriers.

Personnel Receiving Pay from this Grant at Any Point in the Project:

	Year 1	**Year 2**	**Year 3**	**NCE**
Fergus J. Couch, Ph.D.	7.33%	8.17%	7.50%	6.58%

Gaofeng Cui, Ph.D.	20.83%	
Susan Slager, Ph.D.	2.83%	
Xianshu Wang, Ph.D.		12.5%

NOTE: Informatics and statistics personnel are not itemized here because they were billed as Internal Services at a departmental charge-out rate rather than receiving individual salary support.

4. Key Research Accomplishments:

- Genome wide associations studies have identified 27 modifiers of ovarian cancer risk among *BRCA1* carriers.
- A modifier locus on chromosome 4q32 is unique to *BRCA1* carriers.
- Altered expression of *ABHD8* and *ANKLE1* account for the increased ovarian cancer risk associated with common variants on chromosome 19p13.1.
- Personalized ovarian cancer risk prediction models for *BRCA1* carriers identified women with lifetime risks ranging from 28% to 63%.
- Risks of ovarian cancer associated with *BRCA1* mutations are modified by the position of the mutation in the *BRCA1* gene.

5. Conclusion:

In summary, we have completed multiple phases of GWAS aimed at identifying ovarian cancer risk modifiers among *BRCA1* mutation carriers. We showed that variants from 25 loci that have been associated with risk of ovarian cancer in the general population are risk modifiers of ovarian cancer for *BRCA1* mutation carriers. In addition, two novel loci at 4q32 and 17q21 have been associated with ovarian cancer risk in *BRCA1* carriers but not in the general population. Of these the 4q32 locus was not associated with ovarian cancer in *BRCA2* mutation carriers. Thus, specific modifiers of ovarian cancer risk exist for this population. The 27 risk modifiers of ovarian cancer risk are useful for predicting differences in individual ovarian cancer risk among *BRCA1* mutation carriers. Estimation of personalized risks of ovarian cancer for BRCA1 mutation carriers will be made available in the Boadicea risk prediction program.

6. Publications, Abstracts, and Presentations:

1. Lay Press: Nothing to Report

2. 2. Peer Reviewed Scientific Journals

Note: There are many publications resulting from this grant beyond those referenced in this report (see Publications, Abstracts, and Presentations). Funding from the grant was used to design the iCOGS and Oncoarray custom genotyping arrays, and was used to cover the cost of genotyping BRCA1 carrier DNA samples for the GWAS, iCOGS, and Oncoarray projects. Any manuscript using these arrays or using data derived from genotyping studies of BRCA1 carriers using these arrays was required to acknowledge the grant.

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3. Invited Articles: Nothing to Report.

4. Abstracts: Nothing to Report

7. Inventions, Patents, and Licenses:

Nothing to report.

8. Reportable Outcomes:

Products related scientific advance

A total of 27 genetic modifiers of ovarian cancer risk among BRCA1 mutation carriers have been identified.

A modifier locus on chromosome 4q32 specifically influences risks of ovarian cancer among BRCA1 mutation carriers and not among the general population or BRCA2 mutation carriers.

Risk loci associated with specific subtypes of ovarian cancer have been identified, suggesting unique etiological pathways for the histological subtypes of ovarian cancer.

The ovarian cancer risk loci explain 6.4% of the excess familial relative risk of epithelial ovarian cancer in the general population.

Personalized ovarian cancer risk prediction models for BRCA1 carriers developed using the identified risk loci identify BRCA1 mutation carriers with absolute ovarian cancer risks by age 80 ranging from 28% to 63%.

Position dependent risks of ovarian cancer for different BRCA1 and BRCA2 mutations have been determined that can be used in clinical risk prediction models.

9. Other Achievements:

Nothing to report.

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11. Appendices

The Appendicies consist of copies of each of the publications originating from our group which are referenced in this report.

Ramus et al., 2012
Couch et al., 2012
Couch et al., 2013
Permuth-Wey et al., 2013
Kuchenbaecker et al., 2015
Rebbeck et al., 2015

RESEARCH ARTICLE

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Ovarian Cancer Susceptibility Alleles and Risk of Ovarian Cancer in *BRCA1* and *BRCA2* Mutation Carriers

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Additional Supporting Information may be found in the online version of this article.

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ABSTRACT: Germline mutations in *BRCA1* and *BRCA2* are associated with increased risks of breast and ovarian cancer. A genome-wide association study (GWAS) identified six alleles associated with risk of ovarian cancer for women in the general population. We evaluated four of these loci as potential modifiers of ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. Four single-nucleotide polymorphisms (SNPs), rs10088218 (at 8q24), rs2665390 (at 3q25), rs717852 (at 2q31), and rs9303542 (at 17q21), were genotyped in 12,599 *BRCA1* and 7,132 *BRCA2* carriers, including 2,678 ovarian cancer cases. Associations were evaluated within a retrospective cohort approach. All four loci were associated with ovarian cancer risk in *BRCA2* carriers; rs10088218 per-allele hazard ratio (HR) = 0.81 (95% CI: 0.67–0.98) P-trend = 0.033, rs2665390 HR = 1.48 (95% CI: 1.21–1.83) P-trend = 1.8×10^{-4}, rs717852 HR = 1.25 (95% CI: 1.10–1.42) P-trend = 6.6×10^{-4}, rs9303542 HR = 1.16 (95% CI: 1.02–1.33) P-trend = 0.026. Two loci were associated with ovarian cancer risk in *BRCA1* carriers; rs10088218 per-allele HR = 0.89 (95% CI: 0.81–0.99) P-trend = 0.029, rs2665390 HR = 1.25 (95% CI: 1.10–1.42) P-trend = 6.1×10^{-4}. The HR estimates for the remaining loci were consistent with odds ratio estimates for the general population. The identification of multiple loci modifying ovarian cancer risk may be useful for counseling women with *BRCA1* and *BRCA2* mutations regarding their risk of ovarian cancer.

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KEY WORDS: ovarian cancer; BRCA1; BRCA2; association; SNP

Introduction

Pathogenic mutations in the *BRCA1* (MIM# 113705) and *BRCA2* (MIM# 600185) genes confer high risks of ovarian and breast cancer [Miki et al., 1994; Wooster et al., 1995]. Breast cancer risks by age 70 have been estimated to range between 40% and 87% for *BRCA1* and 40–84% for *BRCA2* mutation carriers, whereas

ovarian cancer risk estimates range between 16–68% and 11–27% for *BRCA1* and *BRCA2* mutation carriers, respectively [Antoniou et al., 2003; Antoniou et al., 2008; Begg et al., 2008; Chen et al., 2006; Ford et al., 1998; Hopper et al., 1999; Milne et al., 2008; Simchoni et al., 2006; Struewing et al., 1997; Thompson et al., 2001; Thompson et al., 2002]. Recent genome-wide association studies (GWAS) have identified common alleles associated with risk of breast, ovarian, and other cancers [reviewed Easton and Eeles, 2008; McCarthy and Hirschhorn, 2008; Song et al., 2009]. These common variants are plausible candidates for modifiers of disease risk for mutation carriers. The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) has provided convincing evidence that variants identified through GWAS of breast cancer are also associated with the risk of developing breast cancer for *BRCA1* and/or *BRCA2* mutation carriers [Antoniou et al., 2008a; Antoniou et al., 2009; Antoniou et al., 2010b; Antoniou et al., 2011].

Similarly, CIMBA has investigated the influence of ovarian cancer GWAS variants on ovarian cancer risk in *BRCA1* and *BRCA2* carriers. The first ovarian cancer susceptibility locus identified by a GWAS was rs3814113 at 9p22.2. The minor C allele was associated with a decreased risk of ovarian cancer (odds ratio (OR) = 0.82, 95% confidence interval (CI): 0.79–0.86, $P = 5.1 \times 10^{-19}$) [Song et al., 2009]. A previous CIMBA study showed that the minor allele of rs3814113 was also associated with a reduced risk of ovarian cancer for both *BRCA1* and *BRCA2* carriers (HR = 0.78 for both *BRCA1* and *BRCA2* mutation carriers) [Ramus et al., 2011].

A breast cancer GWAS in *BRCA1* mutation carriers found that locus 19p13 is associated with breast cancer risk for *BRCA1* mutation carriers. Two alleles on 19p13, rs8170C>T and rs2363956G>T, showed independent associations with breast cancer risk [Antoniou et al., 2010a]. Analysis of the associations of these SNPs with ovarian cancer risk in 843 ovarian cancer cases showed no evidence that this locus modifies ovarian cancer risk for *BRCA1* mutation carriers. However, the same two alleles were identified at the same time as ovarian cancer susceptibility alleles in a population-based ovarian cancer GWAS - rs8170 (OR = 1.12, 95% CI: 1.07–1.17, P-trend = 3.6×10^{-6}, serous OR = 1.18, 95% CI: 1.12–1.25, P-trend = 2.7×10^{-9}) and rs2363956 (OR = 1.1, 95% CI: 1.06–1.15, P-trend = 1.2×10^{-7}, serous OR = 1.16, 95% CI: 1.11–1.21, P-trend = 3.8×10^{-11}) [Bolton et al., 2010]. Subsequent genotyping of SNPs rs8170 and rs67397200 (an SNP correlated with both rs8170 and rs2363956 and identified via imputation), in a larger series of *BRCA1* and *BRCA2* mutation carriers from CIMBA, confirmed that both SNPs are associated with breast cancer risk. This analysis, which included 1,399 *BRCA1* ovarian cancer cases and 428 *BRCA2* ovarian cancer cases, also found that the 19p13 SNPs were associated with ovarian cancer risk in both *BRCA1* and *BRCA2* carriers in an analysis of the simultaneous breast and ovarian cancer associations in *BRCA1* carriers [Couch et al., in press].

Four additional ovarian cancer susceptibility loci were identified in a GWAS of more than 10,000 cases and 17,000 controls: rs2072590G>T (2q31) OR = 1.16 (95% CI: 1.12–1.21) P-trend = 4.5×10^{-14}, rs2665390T>C (3q25) OR = 1.19 (95% CI: 1.11–1.27) P-trend = 3.2×10^{-7}, rs10088218G>A (8q24) OR = 0.84 (95% CI: 0.80–0.89) P-trend = 3.2×10^{-9}, and rs9303542A>G (17q21) OR = 1.11 (95% CI: 1.06–1.16) P-trend = 1.4×10^{-6} [Goode et al., 2010]. All these associations were stronger for serous ovarian cancer, the most common histology observed in BRCA-related ovarian cancer, than for all histologies. To investigate whether these SNPs are associated with risk of ovarian and breast cancer for mutation carriers, we genotyped these SNPs (or, in the case of rs2072590, a surrogate SNP, rs717852A>G, $r^2 = 0.96$) for 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers from 40 studies that were part of CIMBA.

Materials and Methods

Subjects

All subjects were female carriers of pathogenic mutations in *BRCA1* or *BRCA2* from 40 studies from Europe, North America, South Africa, and Australia (Supp. Table S1). Pathogenic mutations were defined as protein-truncating mutations or mutations listed on the Breast Cancer Information Core (BIC) http://research.nhgri.nih.gov/bic/ as described previously [Antoniou et al., 2007]. All subjects were 18 years or older at recruitment. The majority of carriers (>97%) were recruited through cancer genetics clinics offering genetic testing, and enrolled into national or regional studies. Some carriers were identified by population-based sampling of cases, and some by community recruitment. Only women of self-reported white, European ancestry were included in the analysis. Subjects were excluded if they were from a country other than the country in which the study is conducted, or if they carried mutations in both genes. If a woman was enrolled in two different studies, only one of the samples was included in the analysis. These duplicate samples were identified by dates of birth and diagnosis and from available genotyping data. Subject information included year of birth; age at last follow-up; ages at breast and/or ovarian cancer diagnosis; and age at bilateral prophylactic mastectomy or oophorectomy. Related subjects were identified through a unique family identifier. *BRCA1* mutations were classified based on their predicted functional consequence. Class 1 was comprised of loss of function mutations subject to nonsense-mediated decay whereas class 2 mutations were those expected to generate a stable protein (details described previously [Antoniou et al., 2008a]). Subjects participated in clinical or research studies at the host institutions under ethically-approved protocols. Further details about CIMBA are described elsewhere [Chenevix-Trench et al., 2007].

Genotyping

The DNA samples from 12,599 *BRCA1* and 7,132 *BRCA2* carriers from 40 studies were genotyped for SNPs rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) using the iPLEX (Sequenom, San Diego, CA) Mass Array platform (Supp. Table S1) at four genotyping centers. We used a correlated SNP ($r^2 = 0.96$), rs717852, to replace a failed assay for rs2072590. All genotyping data were subjected to a standard set of quality control criteria. Samples from affected and unaffected subjects were randomly arrayed within plates. No template controls were included on every 384-well plate and at least 2% of the samples were tested in duplicate. Samples were excluded if they consistently failed genotyping, defined as a pass rate of < 80% for all SNPs in this genotyping round. For a study to be included in the analysis, the genotype data were required to attain or exceed a call-rate threshold of 95% and a concordance between duplicates of 98%. We also evaluated the deviation from Hardy-Weinberg equilibrium (HWE) for unrelated subjects. For none of these studies was HWE rejected at a predefined threshold of $P = 0.001$. An additional quality control criterion was consistent results for 95 DNA samples from a standard test plate (Coriell Institute, Camden, NJ) genotyped at all centers. If the genotyping was inconsistent for more than one sample in the test plate, the study was excluded. A total of 19,731 carriers with genotype data were eligible for inclusion in the analysis (12,599 *BRCA1* and 7,132 *BRCA2* carriers) (Supp. Table S1). Three studies failed quality control for rs717852 and one for rs2665390.

Table 1. Summary Characteristics for the 19,731 Eligible *BRCA1* and *BRCA2* Carriers[a] Used in the Analysis

	BRCA1		*BRCA2*	
Characteristic	Unaffected	Ovarian cancer	Unaffected	Ovarian cancer
Number	10,535	2,064	6,518	614
Person-years follow-up	459,178	104,942	304,789	34,605
Median age at censure (IQR)	42 (35–50)	50 (45–56)	45 (38–55)	56 (49–63)
Age at censure, N (%)				
< 30	1,536 (14.6)	93 (4.5)	796 (12.2)	24 (3.9)
30–39	2,945 (28.0)	171 (8.3)	1,402 (21.5)	15 (2.4)
40–49	3,375 (32.0)	760 (36.8)	2,017 (31.0)	129 (21.0)
50–59	1,721 (16.3)	707 (34.8)	1,297 (19.9)	217 (35.3)
60–69	656 (6.2)	269 (13.0)	667 (10.2)	175 (28.5)
70+	302 (2.9)	64 (3.1)	339 (5.2)	54 (8.8)
Year of birth, N (%)				
<1920	50 (0.5)	8 (0.4)	56 (0.9)	11 (1.8)
1920–1929	204 (1.9)	123 (6.0)	199 (3.1)	67 (10.9)
1930–1939	548 (5.2)	337 (16.3)	499 (7.7)	163 (26.6)
1940–1949	1,495 (14.2)	678 (32.9)	1,122 (17.2)	323 (37.8)
1950–1959	2,757 (26.2)	641 (31.1)	1,736 (26.6)	115 (18.7)
1960–1969	3,113 (29.6)	256 (12.4)	1,747 (26.8)	23 (3.8)
1970+	2,368 (22.5)	21 (1.0)	1,159 (17.8)	3 (0.5)
Mutation class, N (%)				
Class 1[b]	6,460 (61.3)	1,481 (71.8)	6,058 (92.9)	576 (93.8)
Class 2[b]	3,294 (31.3)	459 (22.2)	163 (2.5)	9 (1.5)
Other	781 (7.4)	124 (6.0)	297 (4.6)	29 (4.7)

[a]Carriers of self-reported white European ancestry only.
[b]See methods for definitions.
IQR, interquartile range.

Statistical Analysis

The primary aim of this study was to evaluate the association between each genotype and ovarian cancer risk. The primary endpoint was therefore the age at diagnosis of ovarian cancer. For this purpose, individuals were censored at the age of the ovarian cancer diagnosis, or risk-reducing salpingo-oophorectomy (RRSO) or the age at last observation. Breast cancer was not considered as a censoring event in this analysis, and mutation carriers who developed ovarian cancer after a breast cancer diagnosis were considered as affected in the ovarian cancer analysis. To address the fact that mutation carriers were not sampled at random with respect to their disease phenotype, analysis was conducted by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes as previously described [Antoniou et al., 2007; Barnes et al., In Press]. This method has been shown to provide unbiased estimates of the risk ratios within the present sampling frame [Barnes et al., In Press]. The effect of each SNP was modeled either as a per-allele hazard ratio (HR) (multiplicative model) or as separate HRs for heterozygotes and homozygotes, and these were estimated on the logarithmic scale. The HRs were assumed to be independent of age (i.e., we used a Cox proportional-hazards model). The assumption of proportional hazards was tested by adding a "genotype x age" interaction term to the model in order to fit models in which the HR changed with age. Analyses were carried out with the pedigree-analysis software MENDEL [Lange et al., 1988] and details of this approach have been described previously [Antoniou et al., 2007; Barnes et al., In Press]. We examined between study/country heterogeneity by comparing the models that allowed for study-specific log HRs against models in which the same log HR was assumed to apply to all studies.

To investigate whether our results were influenced by any of our assumptions, we performed additional sensitivity analyses. If any of the SNPs were associated with disease survival, the inclusion of prevalent cases may influence the HR estimates. We therefore repeated our analysis by excluding mutation carriers diagnosed more than 5 years prior to the age at recruitment into the study. We also examined whether SNP associations differed by type of *BRCA1* mutations as described above.

The associations of these SNPs with breast cancer risk were assessed within a competing risk analysis framework [Barnes et al., In Press; Ramus et al., 2011] by estimating HRs simultaneously for breast and ovarian cancers. In this model, each individual was at risk of developing either breast or ovarian cancer, and the probabilities of developing each disease were assumed to be independent conditional on the underlying genotype. A different censoring process was used in this case, whereby individuals were followed up to the age of the first breast or ovarian cancer diagnosis and were considered to have developed the corresponding disease. No follow-up was considered after the first cancer diagnosis. Individuals were censored for breast cancer at the age of bilateral prophylactic mastectomy and for ovarian cancer at the age of bilateral oophorectomy and in such circumstances were assumed to be unaffected for the corresponding disease. The remaining individuals were censored at the age at last observation and were assumed to be unaffected for both diseases.

To ensure a sufficiently large number of mutation carriers within each stratum, we grouped studies from the same country. All analyses were stratified and used calendar year and cohort-specific cancer incidences for *BRCA1* and *BRCA2* [Antoniou et al., 2008b]. For sensitivity analyses, strata with small numbers of mutation carriers were grouped. We used a robust variance-estimation approach to allow for the nonindependence among related carriers [Boos, 1992].

Results

In total, 12,599 *BRCA1* and 7,132 *BRCA2* carriers were eligible for analysis of associations between ovarian cancer risk and rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21). The primary analysis included 2,678 mutation carriers who were followed up to the age at diagnosis of invasive ovarian cancer (cases) and 17,053 carriers who were censored as unaffected (Table 1).

Table 2. SNP Genotype Distributions and Associations with Ovarian Cancer Risk

Mutation	Genotype	Unaffected N (%)	Affected[a] N (%)	HR	95% CI	*P*-value
8q24–rs10088218						
BRCA1	GG	7,978 (76.1)	1,574 (76.3)	1		
	AG	2,325 (22.2)	461 (22.4)	0.93	0.83–1.05	
	AA	176 (1.7)	27 (1.3)	0.61	0.41–0.91	
	2-df test					0.032
	per allele			0.89	0.81–0.99	0.029
BRCA2	GG	4,865 (74.7)	485 (79.0)	1		
	AG	1,537 (23.6)	116 (18.9)	0.73	0.59–0.91	
	AA	113 (1.7)	13 (2.1)	1.12	0.61–2.04	
	2-df test					0.014
	per allele			0.81	0.67–0.98	0.033
3q25–rs2665390						
BRCA1	TT	8,242 (85.6)	1,623 (83.1)	1		
	TC	1,330 (13.8)	314 (16.1)	1.25	1.08–1.44	
	CC	58 (0.6)	17 (0.9)	1.57	0.91–2.69	
	2-df test					2.7×10^{-3}
	per allele			1.25	1.10–1.42	6.1×10^{-4}
BRCA2	TT	5,226 (85.3)	449 (78.6)	1		
	TC	862 (14.1)	118 (20.7)	1.58	1.26–1.98	
	CC	38 (0.6)	4 (0.7)	1.20	0.34–4.19	
	2-df test					3.2×10^{-4}
	per allele			1.48	1.21–1.83	1.8×10^{-4}
2q31–rs717852						
BRCA1	TT	4,134 (47.0)	863 (45.3)	1		
	CT	3,807 (43.2)	862 (45.3)	1.11	0.99–1.23	
	CC	864 (9.8)	179 (9.4)	1.06	0.88–1.27	
	2-df test					0.18
	per allele			1.06	0.98–1.14	0.16
BRCA2	TT	3,029 (48.6)	245 (42.0)	1		
	CT	2,645 (42.4)	272 (46.6)	1.30	1.08–1.56	
	CC	558 (9.0)	67 (11.5)	1.51	1.13–2.01	
	2-df test					3.2×10^{-3}
	per allele			1.25	1.10–1.42	6.6×10^{-4}
17q21–rs9303542						
BRCA1	TT	5,695 (54.2)	1,076 (52.3)	1		
	TC	4,085 (38.9)	826 (40.1)	1.08	0.98–1.20	
	CC	729 (6.9)	157 (7.6)	1.15	0.95–1.40	
	2-df test					0.17
	per allele			1.08	1.00–1.17	0.06
BRCA2	TT	3,445 (53.0)	296 (48.3)	1		
	TC	2,593 (39.9)	264 (43.1)	1.19	1.00–1.42	
	CC	462 (7.1)	53 (8.7)	1.31	0.95–1.81	
	2-df test					0.082
	per allele			1.16	1.02–1.33	0.026

[a]Ovarian cancer.
Analysis restricted to mutation carriers of white European ancestry.

The minor allele of rs2665390 (3q25) was associated with a significantly increased risk of ovarian cancer for both *BRCA1* carriers (per-allele HR = 1.25, 95% CI: 1.10–1.42, P-trend = 6.1×10^{-4}) and *BRCA2* carriers (per allele HR = 1.48, 95% CI: 1.21–1.83, P-trend = 1.8×10^{-4}) (Table 2). The minor allele of rs10088218 (8q24) was associated with a significantly decreased risk of ovarian cancer for both *BRCA1* carriers (per-allele HR = 0.89, 95% CI: 0.81–0.99, P-trend = 0.029), and *BRCA2* carriers (per allele HR = 0.81, 95% CI: 0.67–0.98, P-trend = 0.033). The two remaining SNPs, rs717852 (2q31) and rs9303542 (17q21), were associated with ovarian cancer risk for *BRCA2* carriers (rs717852-per allele HR = 1.25, 95% CI: 1.10–1.42, P-trend = 6.6×10^{-4}; rs9303542-per allele HR = 1.16, 95% CI: 1.02–1.33, P-trend = 0.026). The estimated HRs in *BRCA1* carriers for these two SNPs were also >1 but not significantly different from 1, nor did they differ significantly from the HRs in *BRCA2* carriers. There was no evidence that the HRs varied by age for either *BRCA1* or *BRCA2* mutation carriers (*BRCA1*-rs10088218 $P = 0.34$, rs2665390 $P = 0.24$, rs717852 $P = 0.09$, rs9303542 $P = 0.58$; *BRCA2*-rs10088218 $P = 0.66$, rs2665390 $P = 0.95$, rs717852 $P = 0.88$, rs9303542 $P = 0.67$). The country-specific HRs are shown in Figure 1. There was no evidence of heterogeneity in HRs across the studies/countries (*BRCA1*-rs10088218 $P = 0.27$, rs2665390 $P = 0.59$, rs717852 $P = 0.60$, rs9303542 $P = 0.10$; *BRCA2* -rs10088218 $P = 0.16$, rs2665390 $P = 0.32$, rs717852 $P = 0.75$, rs9303542 $P = 0.49$).

To determine if any survival bias was introduced by including long-term survivors, we excluded all ovarian cancer cases recruited 5 or more years after diagnosis (Supp. Table S2). All HR estimates were similar to those from the primary analysis although only three were significant in the reduced sample set.

We examined the associations between the SNPs and ovarian cancer risk by the *BRCA1* mutation-type based on the predicted functional consequence (Supp. Table S2). We found no evidence of a difference in the per-allele HR by *BRCA1* mutation type for rs10088218 (8q24) (P for difference in HR = 0.99). For rs2665390 (3q25) the estimated HR for class 1 mutations was somewhat higher (per-allele HR = 1.34 [95% CI: 1.15-1.56] P-trend = 2.2×10^{-4})

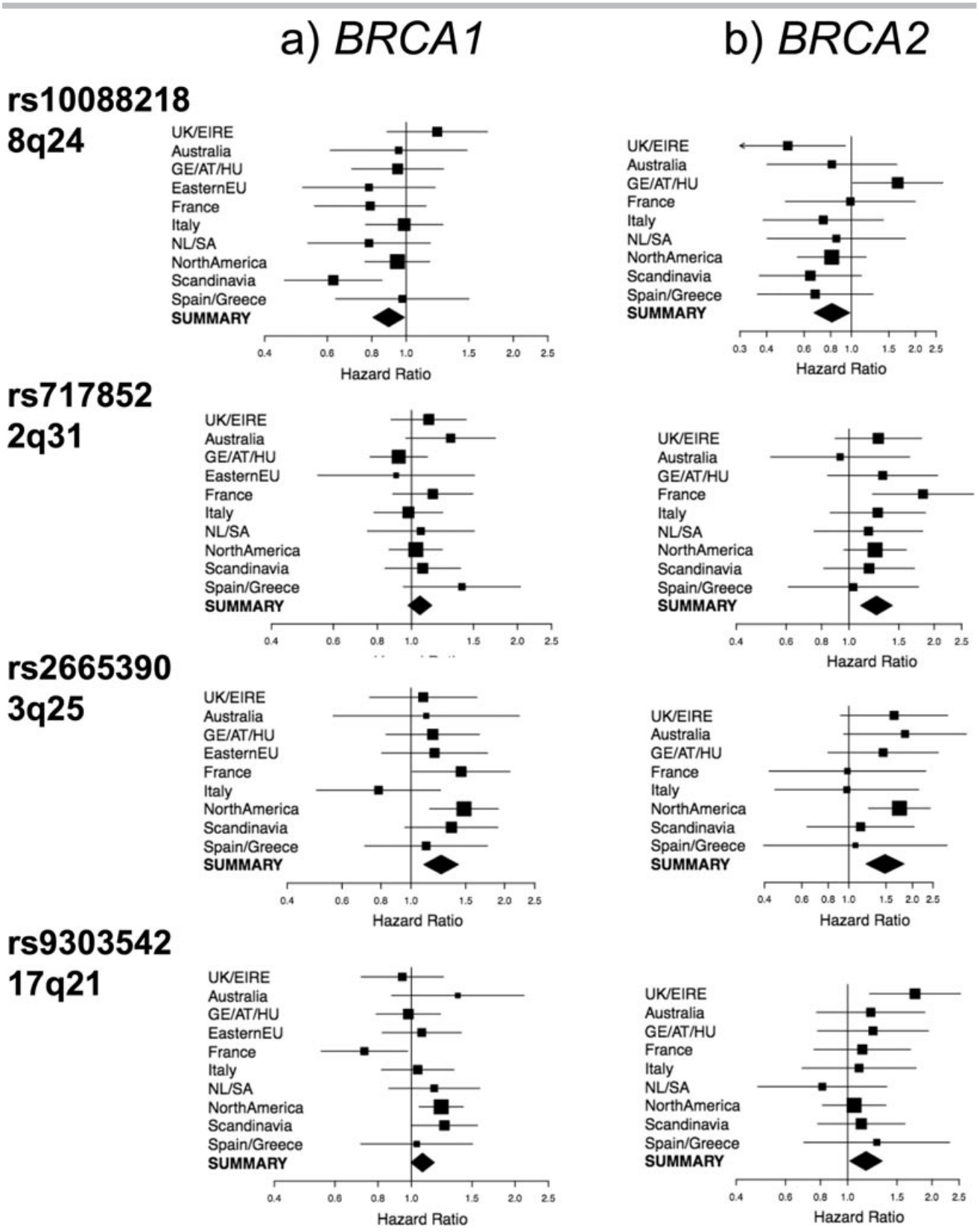

Figure 1. Forest plots of study-specific HRs for ovarian cancer risk in (a) *BRCA1* mutation carriers, (b) *BRCA2* mutation carriers. Country-specific per-allele HR estimates for the SNPs rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) in *BRCA1* and *BRCA2* mutation carriers. The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% confidence intervals. Diamonds indicate the summary HR estimates for all of the CIMBA. For *BRCA2,* some of the smaller studies have been combined with others from the same country. GE/AT/HU denotes the stratum for Germany, Austria, and Hungary. NL/SA denotes the stratum for the Netherlands and South Africa.

Table 3. Competing Risk Analysis

					Breast cancer			Ovarian cancer		
		Unaffected N (%)	Breast cancer N (%)	Ovarian cancer N (%)	HR	95% C.I.	*P*-value	HR	95% C.I.	*P*-value
8q24—rs10088218										
BRCA1	GG	3,661 (77.0)	4,772 (75.5)	1,119 (76.4)	1			1		
	AG	1,025 (21.5)	1,431 (22.6)	330 (22.5)	1.03	0.94–1.11		0.96	0.83–1.11	
	AA	70 (1.5)	117 (1.9)	16 (1.1)	1.08	0.84–1.38		0.55	0.32–0.94	
	2-df test						0.72			0.083
	per allele				1.03	0.96–1.10	0.44	0.91	0.80–1.03	0.13
BRCA2	GG	2,123 (73.9)	2,861 (75.3)	366 (80.6)	1			1		
	AG	699 (24.3)	877 (23.1)	77 (17.0)	0.91	0.82–1.02		0.60	0.46–0.78	
	AA	53 (1.8)	62 (1.6)	11 (2.4)	0.85	0.61–1.18		1.17	0.60–2.27	
	2-df test						0.17			7.7×10^{-4}
	per allele				0.92	0.84–1.00	0.061	0.72	0.57–0.91	5.7×10^{-3}
3q25–rs2665390										
BRCA1	TT	3,716 (85.2)	4,995 (85.7)	1,151 (82.8)	1			1		
	TC	614 (14.1)	801 (13.7)	229 (16.4)	1.00	0.90–1.11		1.27	1.06–1.51	
	CC	31 (0.7)	33 (0.6)	11 (0.8)	0.80	0.53–1.19		1.22	0.62–2.41	
	2-df test						0.54			0.028
	per allele				0.98	0.89–1.08	0.70	1.23	1.06–1.44	8.5×10^{-3}
BRCA2	TT	2,282 (85.5)	3,067 (85.1)	326 (76.8)	1			1		
	TC	368 (13.8)	517 (14.4)	95 (22.5)	1.02	0.89–1.16		1.75	1.34–2.27	
	CC	19 (0.7)	20 (0.6)	3 (0.7)	0.72	0.39–1.35		1.02	0.21–5.10	
	2-df test						0.57			1.6×10^{-4}
	per allele				0.99	0.87–1.12	0.82	1.59	1.25–2.02	1.9×10^{-4}
2q31–rs717852										
BRCA1	TT	1,817 (47.3)	2,576 (46.5)	606 (45.5)	1			1		
	CT	1,667 (43.5)	2,400 (43.3)	602 (45.1)	1.01	0.94–1.09		1.10	0.96–1.25	
	CC	356 (9.3)	562 (10.2)	125 (9.4)	1.13	0.99–1.29		1.10	0.87–1.40	
	2-df test						0.18			0.32
	per allele				1.04	0.99–1.10	0.14	1.08	0.98–1.19	0.15
BRCA2	TT	1,345 (49.8)	1,752 (47.5)	177 (41.4)	1			1		
	CT	1,112 (41.2)	1,603 (43.5)	202 (47.2)	1.08	0.98–1.19		1.39	1.11–1.74	
	CC	244 (9.0)	331 (9.0)	50 (11.5)	1.03	0.87–1.21		1.60	1.13–2.26	
	2-df test						0.30			3.8×10^{-3}
	per allele				1.04	0.97–1.12	0.30	1.31	1.12–1.53	8.5×10^{-4}
17q21–rs9303542										
BRCA1	TT	2,537 (53.1)	3,470 (54.8)	764 (52.3)	1			1		
	TC	1,891 (39.6)	2,434 (38.5)	586 (40.1)	0.98	0.91–1.05		1.08	0.95–1.23	
	CC	349 (7.3)	426 (6.7)	111 (7.6)	0.95	0.82–1.09		1.10	0.87–1.40	
	2-df test						0.70			0.44
	per allele				0.98	0.92–1.03	0.41	1.06	0.97–1.17	0.22
BRCA2	TT	1,517 (52.8)	2,012 (53.1)	212 (46.7)	1			1		
	TC	1,136 (39.6)	1,520 (40.1)	203 (44.9)	0.98	0.89–1.08		1.26	1.02–1.55	
	CC	218 (7.6)	259 (6.8)	38 (8.4)	0.87	0.73–1.05		1.17	0.79–1.74	
	2-df test						0.35			0.099
	per allele				0.96	0.89–1.03	0.22	1.16	0.99–1.35	0.075

Associations with breast and ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. Analysis restricted to mutation carriers of European ancestry.

compared to class 2 mutations (HR = 1.08 (95% CI: 0.78–1.36), P-trend = 0.85), but the difference in HRs was not significant (P = 0.06). Similar patterns in the HRs between class 1 and class 2 mutations were seen for rs9303542 (17q21) and rs717852 (2q31), but none of the differences were significant (P = 0.20 and P = 0.36, respectively).

To determine whether these four SNPs were also associated with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers, we performed an analysis in which we estimated HRs for breast and ovarian cancer simultaneously within a bivariate outcome model (Table 3). There was no evidence of association between these SNPs and breast cancer risk for mutation carriers. The estimated HRs for ovarian cancer risk under this analysis were similar to those estimated in the main analysis. However, some of the results were no longer significant due to the fact that mutation carriers diagnosed with ovarian cancer after a breast cancer diagnosis are censored at breast cancer, which results in a reduced number of ovarian cancer cases. The 3q25 SNP, rs2665390, was significantly associated with ovarian cancer risk for both *BRCA1* and BRCA2 carriers (per-allele HR = 1.23, 95% CI: 1.06-1.44, P-trend = 8.5×10^{-3} and per-allele HR = 1.59, 95% CI: 1.25–2.02, P-trend = 1.9×10^{-4}, respectively). As in the primary analysis, rs717852 (2q31) was only associated with an increased ovarian cancer risk in *BRCA2* carriers (HR = 1.31, 95% CI: 1.12–1.53, P-trend = 8.5×10^{-4}). The magnitude of the association between SNP rs10088218 (8q24) and ovarian cancer risk in *BRCA2* carriers was somewhat larger than in the primary analysis (HR = 0.72, 95% CI: 0.57–0.91, P-trend = 5.7×10^{-3}).

Discussion

Recent studies have shown that common genetic variants identified from ovarian cancer GWAS are associated with susceptibility to ovarian cancer for *BRCA1* and/or *BRCA2* mutation carriers [Couch et al., in press; Ramus et al., 2011]. In the present study, we genotyped four SNPs, rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) that were found to be associated with ovarian cancer in women from the general population. We found

that all SNPs were associated with ovarian cancer risk for *BRCA2* mutation carriers. There was significant evidence that two of the SNPs (rs10088218 at 8q24 and rs2665390 at 3q25) were also associated with ovarian cancer risk for *BRCA1* mutation carriers. For the remaining two SNPs at 2q31 and 17q21, the associations with ovarian cancer risk in *BRCA1* mutations did not reach statistical significance. However, the estimated HRs were still consistent with both the estimated HRs in *BRCA2* carriers, and the estimated ORs in the general population. Thus these data, combined with those for the previously detected ovarian cancer risk SNPs at 9p22.2 [Ramus et al., 2011] and 19p13 [Couch et al, in press], indicate that all six known common susceptibility loci for ovarian cancer, are also associated with the ovarian cancer risk in *BRCA1* and *BRCA2* carriers, and moreover that the relative risk of ovarian cancer is generally similar to that in the general population.

In the general population, the magnitude of the associations with ovarian cancer risk were stronger for cases with the serous histological subtype for rs2072590 (2q31) $P_{heterogeneity} = 2.9 \times 10^{-4}$, rs10088218 (8q24) $P_{heterogeneity} = 1.1 \times 10^{-7}$, and rs2665390 (3q25) $P_{heterogeneity} = 0.02$ [Goode et al., 2010]. However, we were not able to assess this interaction in the *BRCA1* and *BRCA2* carriers, due to small numbers and incomplete pathology data for histological subtype.

When the data were analyzed within a competing risks framework, we observed no evidence that these SNPs were associated with breast cancer risk for *BRCA1* or *BRCA2* mutation carriers. None of the published breast cancer GWAS using women from the general population [Ahmed et al., 2009; Easton et al., 2007; Gold et al., 2008; Hunter et al., 2007; Thomas et al., 2009] have reported associations for these SNPs at the strict genome-wide levels of significance. These results indicate that, for both groups of mutation carriers and for the general population, the predominant association is with ovarian cancer risk and that the association with breast cancer risk, if any, is very weak.

The fine-mapping and functional follow-up of the risk alleles from the ovarian cancer GWAS are currently being performed. Therefore, the gene most likely to be driving the ovarian cancer risk in each region has not yet been identified but the closest genes to each SNP and the genes in the linkage disequilibrium block provide some insight to the potential candidates. The rs2665390 SNP is located at 3q25, and is intronic to the *TIPARP* gene, a member of the poly (ADP-ribose) polymerase (PARP) superfamily. *BRCA1-BRCA2*–deficient cells can use the *PARP1* alternative DNA repair mechanism to survive, and synthetic inhibition of *PARP1* has been developed as a new therapy for breast and ovarian cancer patients with mutations in these genes [Fong et al., 2009]. There are no other candidate genes within 200 kb of this SNP and the five other genes within the linkage disequilibrium block (*LEKR1, LOC730091, PA2G4P4, SSR3,* and *KCNAB1*) are not known to have functions that suggest a role in cancer [www.genecards.org; Safran et al., 2010].

The rs717852 SNP is located at 2q31 in a region containing a family of homeobox (*HOX*) genes; *HOXD10, HOXD11, HOXD12, HOXD13, HOXD3, HOXD4, HOXD8, HOXD9,* and *HOXD1. HOX* genes are involved in regulating embryogenesis and organogenesis and altered expression of *HOX* genes has been reported in many cancers [Buzzai and Licht, 2008; Shiraishi et al., 2002.]. The other genes in this region, *KIAA1715, EVX2,* and *MTX2,* do not have a reported role in cancer [www.genecards.org; Safran et al., 2010]. The ovarian cancer risk-associated SNP rs2072590 is downstream of *HOXD3* and upstream of *HOXD1*, and it tags SNPs in the *HOXD3* 3′ untranslated region. The genotyped SNP rs717852 is intronic of *HOXD3.*

Common variants that confer susceptibility to multiple cancer phenotypes, including prostate, colorectal, breast, and bladder cancers have been identified in a 500-kb region of a gene desert at 8q24, approximately 200 kb 5′ of *MYC* [Jia et al., 2009]. Functional studies have suggested that transcriptional regulation of *MYC* may explain these associations [Jia et al., 2009; Pomerantz et al., 2009]. In contrast, rs10088218 is >700 kb 3′ of *MYC.* Variants in this region may also be capable of distant regulation of *MYC.* However, *PVT1,* a noncoding RNA which is an MYC protein target, is another plausible candidate in this region. *PVT1* is amplified in breast and ovarian tumors, and is overexpressed in transformed cells [Guan et al., 2007]. A prostate cancer risk variant at the 8q24 locus, located 0.5 Mb upstream of the *PVT1* gene has recently been shown to be associated with increased expression of the *PVT1* gene rather than affecting MYC expression [Meyer et al., 2011].

The final SNP, rs9303542 at 17q21, is intronic to *SKAP1*, a src kinase-associated phosphoprotein, which regulates mitotic progression [Fang et al., 2009]. SKAP1 has been shown to suppress activation of *RAS* and *RAF1* genes that may have a role in the early-stage development of ovarian cancer [Kosco et al., 2008]. The region also contains 10 *HOXB* genes and, as described earlier, altered expression of *HOX* genes has been reported in many cancers. Of the other 12 genes in this region, the only ones with a suggested role in cancer are, *PRAC,* encoding a small nuclear protein which is a prostate cancer susceptibility candidate, *CBX1,* which may play an important role in the epigenetic control of chromatin structure and gene expression, and *CDK5RAP3* that may be involved in cell proliferation [www.genecards.org; Safran et al., 2010].

We have previously demonstrated that common risk alleles for breast cancer increase the risk of breast cancer to a similar relative extent in *BRCA1* and *BRCA2* carriers (once estrogen receptor status is taken into account). These results demonstrate that the same holds true for ovarian cancer loci identified through GWAS, and provides a general model in which common susceptibility loci and *BRCA1* and *BRCA2* mutations interact multiplicatively on the risk of developing ovarian cancer [Wacholder et al., 2011]. Although the HR conferred by each locus is modest, the HRs are much larger in combination. These translate to small differences in absolute risk between different genotypes for the vast majority of women at low risk of this disease, but the absolute risk differences for mutation carriers will be much greater. As more genetic modifiers of ovarian cancer risk are identified, in the future, such information combined with other risk factors such as parity and oral contraceptive use could be incorporated into risk prediction algorithms such as BOADICEA [Antoniou et al., 2008b]. This could enable the stratification of mutation carriers into different ovarian cancer risk categories and could potentially be used for guiding the clinical management of mutation carriers with respect to screening or prophylactic surgery.

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Research Article

Common Variants at the 19p13.1 and *ZNF365* Loci Are Associated with ER Subtypes of Breast Cancer and Ovarian Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers

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Abstract

Background: Genome-wide association studies (GWAS) identified variants at 19p13.1 and *ZNF365* (10q21.2) as risk factors for breast cancer among *BRCA1* and *BRCA2* mutation carriers, respectively. We explored associations with ovarian cancer and with breast cancer by tumor histopathology for these variants in mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA).

Methods: Genotyping data for 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers from 40 studies were combined.

Results: We confirmed associations between rs8170 at 19p13.1 and breast cancer risk for *BRCA1* mutation carriers [HR, 1.17; 95% confidence interval (CI), 1.07–1.27; $P = 7.42 \times 10^{-4}$] and between rs16917302 at *ZNF365* (HR, 0.84; 95% CI, 0.73–0.97; $P = 0.017$) but not rs311499 at 20q13.3 (HR, 1.11; 95% CI, 0.94–1.31; $P = 0.22$) and breast cancer risk for *BRCA2* mutation carriers. Analyses based on tumor histopathology showed that 19p13 variants were predominantly associated with estrogen receptor (ER)-negative breast cancer for both *BRCA1* and *BRCA2* mutation carriers, whereas rs16917302 at *ZNF365* was mainly associated with ER-positive breast cancer for both *BRCA1* and *BRCA2* mutation carriers. We also found for the first time that rs67397200 at 19p13.1 was associated with an increased risk of ovarian cancer for *BRCA1* (HR, 1.16; 95% CI, 1.05–1.29; $P = 3.8 \times 10^{-4}$) and *BRCA2* mutation carriers (HR, 1.30; 95% CI, 1.10–1.52; $P = 1.8 \times 10^{-3}$).

Conclusions: 19p13.1 and *ZNF365* are susceptibility loci for ovarian cancer and ER subtypes of breast cancer among *BRCA1* and *BRCA2* mutation carriers.

Impact: These findings can lead to an improved understanding of tumor development and may prove useful for breast and ovarian cancer risk prediction for *BRCA1* and *BRCA2* mutation carriers. *Cancer Epidemiol Biomarkers Prev; 21(4); 645–57. ©2012 AACR.*

Introduction

Genome-wide association studies (GWAS) have been used to identify several loci containing common variants that are associated ($P < 1.0 \times 10^{-7}$) with breast cancer risk in the general population. Variants from 12 of these loci have also been investigated as modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers (1–3). While only variants in *CASP8*, *TOX3*, 2q35, and 6q25.1 have been associated with breast cancer risk in *BRCA1* mutation carriers, variants in *FGFR2*, *TNRC9/TOX3*, *MAP3K1*, *LSP1*, 2q35, *SLC4A7/NEK10*, 5p12, and 1p11.2 loci have been associated with breast cancer in *BRCA2* mutation carriers (1–3). This is consistent with the known associations between these single-nucleotide polymorphisms (SNP) and estrogen receptor (ER) status of breast cancers in the general population (4).

Most recently, a GWAS of *BRCA1* mutation carriers conducted through CIMBA identified 5 SNPs on 19p13 that were associated with breast cancer risk for *BRCA1* mutation carriers (5). Two of these showed independent associations: rs8170 [HR, 1.26; 95% confidence interval (CI), 1.17–1.35; $P_{trend} = 2.3 \times 10^{-9}$] and rs2363956 (HR, 0.84; 95% CI, 0.80–0.89; $P_{trend} = 5.5 \times 10^{-9}$). Imputation analysis of the 19p13 region, using 1000 Genomes Project data, identified several correlated SNPs with more significant associations than rs8170 and rs2363956. The 19p13.1 locus was also found to be associated with ER-negative breast cancer (rs8170: OR, 1.21; $P = 0.003$) and triple-negative breast cancer [tumors lacking expression of ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2); rs8170: OR, 1.28; $P = 1.2 \times 10^{-6}$] in the general population (5). In addition, the 19p13.1 locus has been associated with ovarian cancer in the general population (rs8170: OR, 1.12; $P = 3.6 \times 10^{-6}$; ref. 6) but was not found to be associated with ovarian cancer in *BRCA1* mutation carriers (rs8170: HR, 1.07; $P = 0.33$; ref. 5). A separate GWAS in *BRCA2* mutation carriers identified 2 breast cancer susceptibility alleles [rs16917302 at *ZNF365* (10q21.2): HR, 0.75; 95% CI, 0.66–0.86; $P = 3.8 \times 10^{-5}$; and rs311499 at 20q13.33: HR, 0.72; 95% CI, 0.61–0.85; $P = 6.6 \times 10^{-5}$; ref. 7]. A weakly correlated SNP at the *ZNF365* locus (rs10995190) has also been associated with breast cancer overall (OR, 0.83; $P = 5.1 \times 10^{-15}$) and ER-positive ($P = 4.1 \times 10^{-6}$) but not ER-negative breast cancer in the general population (8).

Here, we genotyped more than 12,000 *BRCA1* and 7,000 *BRCA2* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), for the previously genotyped variant at 19p13.1, rs8170, and one of the imputed SNPs that was found to have a stronger association with breast cancer risk for *BRCA1* mutation carriers (rs67397200). We also genotyped SNPs at *ZNF365* (rs16917302) and 20q13.3 (rs311499) in an effort to verify these loci as risk factors for ovarian cancer and to further validate these loci as risk factors for breast cancer in *BRCA1* and *BRCA2* mutation carriers.

Materials and Methods

Subjects

All mutation carriers participated in clinical or research studies at the host institutions under ethically approved protocols and provided written informed consent.

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Subjects were *BRCA1* and *BRCA2* mutation carriers recruited by 40 study centers in 22 countries and assembled through the CIMBA initiative (Supplementary Table S1). The majority were recruited through cancer genetics clinics and enrolled into national or regional studies. Others were identified in research studies of high-risk families, by population-based sampling of cases and some by community recruitment. Eligibility to participate in CIMBA is restricted to female carriers of pathogenic *BRCA1* or *BRCA2* mutations, defined by generally recognized criteria (Breast Cancer Information Core), who were 18 years old or older at recruitment. Information collected included the year of birth; mutation description (including nucleotide position and base change); age at last follow-up; ages at breast and ovarian cancer diagnoses; and age or date at bilateral prophylactic mastectomy. Information was also available on the country of residence. Related individuals were identified through a unique family identifier. Women with pathogenic mutations in both *BRCA1* and *BRCA2* were excluded from the current analysis. The primary analysis was restricted to women self-reported as "white European." Overlap of carriers between studies was evaluated by comparing the year of birth, exact mutation description, the reported ages, and previous SNP genotype data available within the CIMBA database. Duplicated mutation carriers were included only once in the analysis.

Genotyping

rs311499 at 20q13.3, rs16917302 at *ZNF365*, and both rs8170 and rs67397200 at 19p13.1 were genotyped using the iPLEX Mass Array platform at 4 genotyping centers as part of a larger study of 24 candidate SNPs. All centers included at least 2% duplicate samples and a random mixture of affected and unaffected carriers on each plate. Samples that failed for 5 or more of the SNPs genotyped were excluded from the analysis. Studies with an SNP call rate of <95% were excluded from the analysis of the SNP. The concordance between duplicates had to be at least 98%. To assess the accuracy of genotyping across genotyping centers, all centers genotyped 95 DNA samples from a standard test plate (Coriell Institute, Camden, NJ) for all SNPs. Genotyping centers with more than one concordance failure on the test plate for an SNP were excluded for analyses of that SNP. Deviation from Hardy–Weinberg equilibrium (HWE) was assessed for unrelated subjects separately for each SNP and study. The observed genotype frequencies were not significantly different from those expected under HWE for any of the SNPs and studies. After the above exclusions, a total of 19,731 unique mutation carriers (12,599 *BRCA1* and 7,132 *BRCA2*) from 40 studies had an observed genotype for at least one SNP (Supplementary Table S1).

Tumor pathology data collection

Tumor pathology data were collected from patient pathology reports, medical records, pathology review data, tumor registry records, and results from tissue microarrays. ER status was identified as negative or positive, with immunohistochemistry scoring data and methodology provided when available. Most studies applied a cutoff point of >10% tumor cells stained positive for ER-positive status. For a small number of cases, where other scoring methods based on the proportion and intensity of staining were applied (Allred score, Remmele score, and H-score), widely accepted cutoff points were used. Consistency checks were conducted to validate receptor data against supplementary scoring information if provided.

Statistical analysis

The aim of the primary analysis was to evaluate the association between each genotype and breast cancer risk. We conducted the analysis by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes as previously described (9). The phenotype of each individual was defined by age at diagnosis of breast cancer or age at last follow-up. Individuals were censored at the earliest of age of first breast cancer diagnosis, ovarian cancer diagnosis, bilateral prophylactic mastectomy, or age at last observation. Mutation carriers censored at ovarian cancer diagnosis were considered unaffected in the analysis of breast cancer. The effect of each SNP was modeled either as a per-allele HR (multiplicative model) or as separate HRs for heterozygotes and homozygotes. We used a Cox proportional hazards model and tested the assumption of proportional hazards by adding a "genotype $\times$ age" interaction term to fit models in which the HR changed with age. We examined heterogeneity across studies by comparing models that allowed for study-specific log HRs against models in which the same log HR was assumed to apply to all studies. All analyses were stratified by country of residence and applied cohort-specific breast cancer incidence rates for *BRCA1* and *BRCA2* (10). A robust variance-estimation approach was used to adjust for the nonindependence among related carriers.

To evaluate the evidence of replication for each of the SNPs, analyses were restricted to mutation carriers who had not been used in any of the previous *BRCA1* and *BRCA2* studies. The number of new samples used in each of the SNP analyses is shown in Supplementary Table S2. In addition, analyses were conducted using all available *BRCA1* and *BRCA2* carriers. The combined effects of the SNPs on breast cancer risk were evaluated by fitting retrospective likelihood models while allowing for linkage disequilibrium between the loci. To test for potential effects of survival bias, prevalent cases, defined as mutation carriers diagnosed more than 5 years prior to the age at recruitment, were excluded. Associations with specific functional class of mutation were also assessed. Class 1 mutations are predicted to undergo nonsense-mediated RNA decay resulting in reduced levels of mutant transcript, whereas class 2 mutations are predicted to generate stable mutant proteins (11). The associations with breast cancer subtypes defined by the ER status of the tumors in *BRCA1* and *BRCA2* mutation carriers were assessed by an

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extension of the retrospective likelihood approach that models the simultaneous effect of each SNP on more than one tumor subtype (12). Associations with ovarian cancer risk were evaluated within a competing risk analysis framework (13) by estimating HRs simultaneously for breast and ovarian cancers. Because each mutation carrier was at risk of breast and ovarian cancer, we assumed that the probabilities of developing each disease were independent conditional on the underlying genotype. In this analysis, individuals were followed to the age of the first breast or ovarian cancer diagnosis and were considered to have developed the corresponding disease. Individuals were censored for breast cancer at the age of bilateral prophylactic mastectomy and for ovarian cancer at the age of bilateral oophorectomy and were assumed to be unaffected for the corresponding disease. The remaining individuals were censored at the age at last observation and were assumed to be unaffected for both diseases.

Results

After quality control exclusions, genotype data from 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers including 5,408 *BRCA1* and 3,780 *BRCA2* mutation carriers not studied in the original GWAS were available for analysis. Of the *BRCA1* mutation carriers, 6,390 were affected with breast cancer and 6,209 were considered unaffected in the breast cancer analysis (censored at bilateral prophylactic mastectomy, ovarian cancer, or age at last follow up). Similarly, among the *BRCA2* mutation carriers, 3,810 were affected with breast cancer and 3,322 were unaffected. The characteristics of these mutation carriers are shown in Table 1 and the origins of the samples are summarized in Supplementary Table S1.

The associations between breast cancer risk in *BRCA1* and *BRCA2* mutation carriers and the minor alleles of rs8170 and rs67397200 (19p13.1), rs16917302 (*ZNF365*), and rs311499 (20q13.33) are summarized in Table 2. The minor allele of rs8170 at 19p13.1 was strongly associated with risk of breast cancer in *BRCA1* mutation carriers (HR, 1.20; 95% CI, 1.13–1.28; $P = 8.7 \times 10^{-9}$) but not *BRCA2* mutation carriers. This result for 12,599 *BRCA1* mutation carriers was consistent with the original finding in the *BRCA1* GWAS using 8,363 *BRCA1* mutation carriers (HR, 1.26; 95% CI, 1.17–1.35; $P = 2.3 \times 10^{-9}$). A separate analysis

Table 1. Summary characteristics for the 19,731 eligible *BRCA1* and *BRCA2* mutation carriers used in the analysis

Characteristic	*BRCA1*		*BRCA2*	
	Unaffected	Breast cancer	Unaffected	Breast cancer
Number	6,209	6,390	3,322	3,810
Person-years follow-up	264,903	263,068	147,053	168,201
Median age at Censure (IQR)	42 (34–50)	40 (34–47)	43 (34–53)	43 (37–50)
Age at censure, *n* (%)				
<30	1,189 (19.2)	691 (10.8)	611 (18.4)	306 (8.0)
30–39	1,661 (26.8)	2,445 (38.3)	834 (25.1)	1,141 (30.0)
40–49	1,765 (28.4)	2,191 (34.3)	865 (26.0)	1,394 (36.6)
50–59	1,058 (17.0)	812 (12.7)	566 (17.0)	687 (18.0)
60–69	380 (6.1)	198 (3.1)	302 (9.1)	226 (5.9)
70+	156 (2.5)	53 (0.8)	144 (4.3)	56 (1.5)
Year of birth, *n* (%)				
<1920	28 (0.5)	30 (0.5)	23 (0.7)	44 (1.2)
1920–1929	131 (2.1)	196 (3.1)	99 (3.0)	167 (4.4)
1930–1939	369 (5.9)	516 (8.1)	232 (7.0)	430 (11.3)
1940–1949	832 (13.4)	1,341 (21.0)	458 (13.8)	896 (23.5)
1950–1959	1,409 (22.7)	1,989 (31.1)	691 (20.8)	1,160 (60.5)
1960–1969	1,703 (27.4)	1,666 (26.1)	902 (27.2)	868 (22.8)
1970+	1,737 (28.0)	652 (10.2)	917 (27.6)	245 (6.4)
Mutation class, *n* (%)				
Class 1[a]	4,063 (65.4)	3,878 (60.7)	3,114 (93.7)	3,520 (92.4)
Class 2[a]	1,780 (28.7)	1,973 (30.9)	72 (2.2)	100 (2.6)
Other	366 (5.9)	539 (8.4)	136 (4.1)	190 (5.0)

NOTE: Carriers of self reported European ancestry only.
Abbreviation: IQR, interquartile range.
[a]See Materials and Methods for definitions.

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Table 2. Evaluation of associations between SNPs and breast cancer risk among *BRCA1* and *BRCA2* mutation carriers of European ancestry

SNP/mutation	Genotype	Unaffected, N (%)	Affected,[a] N (%)	HR (95% CI)	*P*
rs8170—19p13.1					
BRCA 1	GG	3,870 (67.5)	3,755 (63.3)	1.00	
	AG	1,689 (29.4)	1,950 (32.9)	1.22 (1.14–1.31)	
	AA	178 (3.1)	227 (3.8)	1.35 (1.13–1.62)	
	Per-allele			1.20 (1.13–1.28)	8.7×10^{-9}
BRCA 2	GG	2,047 (66.3)	2,501 (68.2)	1.00	
	AG	931 (30.2)	1,026 (28.0)	0.93 (0.84–1.03)	
	AA	108 (3.5)	138 (3.8)	1.16 (0.89–1.52)	
	Per-allele			0.98 (0.90–1.07)	0.67
rs67397200—19p13.1					
BRCA 1	CC	2,536 (51.0)	2,455 (46.0)	1.00	
	GC	2,022 (40.6)	2,397 (44.9)	1.24 (1.16–1.34)	
	GG	415 (8.4)	487 (9.1)	1.25 (1.10–1.43)	
	Per-allele			1.17 (1.11–1.23)	2.4×10^{-8}
BRCA 2	CC	1,553 (49.8)	1,871 (50.7)	1.00	
	GC	1,302 (41.7)	1,494 (40.5)	0.95 (0.87–1.04)	
	GG	265 (8.5)	323 (8.8)	1.07 (0.91–1.27)	
	Per-allele			1.00 (0.93–1.07)	0.97
rs311499—20q13.3					
BRCA 1	GG	5,346 (86.2)	5,484 (85.9)	1.00	
	AG	816 (13.2)	873 (13.7)	1.03 (0.94–1.13)	
	AA	41 (0.7)	28 (0.4)	0.67 (0.42–1.08)	
	Per-allele			1.00 (0.91–1.09)	0.94
BRCA 2	GG	2,873 (86.6)	3,312 (87.0)	1.00	
	AG	429 (13.0)	475 (12.5)	0.94 (0.82–1.07)	
	AA	16 (0.5)	21 (0.6)	0.97 (0.60–1.57)	
	Per-allele			0.95 (0.84–1.07)	0.36
rs16917302—10q21.2					
BRCA 1	AA	4,913 (79.3)	5,084 (79.7)	1.00	
	CA	1,216 (19.6)	1,222 (19.2)	0.96 (0.88–1.01)	
	CC	71 (1.1)	73 (1.1)	0.94 (0.69–1.27)	
	Per-allele			0.96 (0.89–1.03)	0.27
BRCA 2	AA	2,583 (77.9)	3,101 (81.5)	1.00	
	CA	691 (20.8)	674 (17.7)	0.82 (0.74–0.92)	
	CC	41 (1.2)	32 (0.8)	0.78 (0.49–1.23)	
	Per-allele			0.83 (0.75–0.93)	7.0×10^{-4}

[a]Breast cancer.

restricted to carriers not used in the *BRCA1* GWAS also confirmed the association (HR, 1.17; 95% CI, 1.07–1.27; $P = 7.42 \times 10^{-4}$; Supplementary Table S2). Similarly, rs67397200 at 19p13.1, which was imputed in the *BRCA1* GWAS, was strongly associated with breast cancer risk in *BRCA1* carriers (HR, 1.17; 95% CI, 1.11–1.23; $P = 2.4 \times 10^{-8}$; Table 2). There was no evidence of heterogeneity in the HRs across studies for *BRCA1* mutation carriers (Fig. 1). However, there was evidence that the per-allele HRs in *BRCA1* mutation carriers for rs8170 ($P = 0.015$) and rs67397200 ($P = 0.007$) at 19p13.1 decreased with increasing age of diagnosis of breast cancer. Because rs8170 and rs67397200 are located in the same region of 19p13.1 ($r^2 = 0.58$), we conducted an analysis for the joint effects of these SNPs on breast cancer risk in *BRCA1* mutation carriers ($n = 10{,}173$). When accounting for haplotype structure, rs67397200 remained significant (P for inclusion $= 2.75 \times 10^{-3}$) and was retained in the model, whereas rs8170 was excluded (P for inclusion $= 0.18$). rs8170 and rs67397200 were not associated with breast cancer risk for *BRCA2* mutation carriers (Table 2).

Among SNPs identified from the original *BRCA2* GWAS, an analysis of genotype data from 7,132 *BRCA2* mutation carriers confirmed that rs16917302 at the *ZNF365* locus was associated with a decreased risk of breast cancer (HR, 0.83; 95% CI, 0.75–0.93; $P = 7.0 \times 10^{-4}$).

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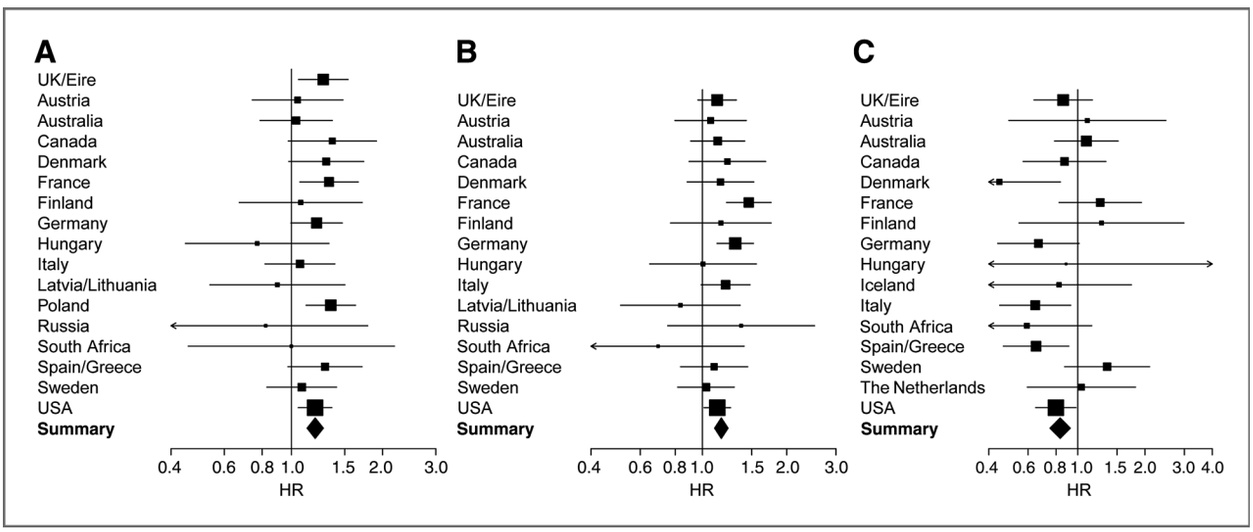

Figure 1. Forest plots of the associations by country of residence of *BRCA1* and *BRCA2* mutation carriers with breast cancer risk overall. A–C, squares indicate the country-specific per-allele HR estimates for SNPs (A) rs8170 for *BRCA1* mutation carriers, (B) rs67397200 for *BRCA1* mutation carriers, and (C) rs16917302 for *BRCA2* mutation carriers. The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% CIs.

The association also replicated in the additional carriers, not previously included in the *BRCA2* GWAS (HR, 0.84; 95% CI, 0.73–0.97; $P = 0.017$; Supplementary Table S2). In contrast, rs311499 from 20q13.3, which was associated with breast cancer risk in the *BRCA2* GWAS (HR, 0.72; 95% CI, 0.61–0.85; $P = 6.6 \times 10^{-5}$; ref. 7), was not associated with risk of breast cancer in *BRCA2* carriers in the overall analysis (HR, 0.95; 95% CI, 0.84–1.07; $P = 0.36$; Table 2), nor the replication study (HR, 1.11; 95% CI, 0.94–1.31; $P = 0.22$; Supplementary Table S2). There was no evidence for heterogeneity in the HRs across studies for *BRCA2* mutation carriers (Fig. 1). HRs for rs16917302 and rs311499 did not vary by age at diagnosis.

To determine whether the inclusion of long-term survivors influenced the results, we repeated our analyses of the 4 SNPs, excluding *BRCA1* and *BRCA2* mutation carriers diagnosed with breast cancer more than 5 years before recruitment (prevalent cases). The strength of the associations for rs16917302 at *ZNF365* (per-allele HR, 0.85) for *BRCA2* mutation carriers and for rs8170 (per-allele HR, 1.19) and rs67397200 at 19p13.1 (per-allele HR, 1.16) for *BRCA1* mutation carriers were essentially unchanged (Supplementary Table S3). There was no influence of mutation type for *BRCA1* mutation carriers on breast cancer risk in the associations between mutations conferring susceptibility to nonsense-mediated RNA decay (NMD; class 1) and missense or truncating mutations not triggering NMD (class 2) for any of the SNPs (Supplementary Table S4).

Breast tumors in *BRCA1* mutation carriers are predominantly ER-negative (14) and rs8170 from 19p13.1 is strongly associated with ER-negative but not ER-positive breast cancer in the general population (5). Because of these previous findings, we evaluated whether rs8170 and rs67397200 at 19p13.1, as well as rs311499 at 20q13.3 and rs16917302 at *ZNF365*, were differentially associated with ER-positive and/or ER-negative tumor status in *BRCA1* and *BRCA2* mutation carriers. Although the stratified results suggested a slightly stronger association for the 19p13.1 rs67397200 SNP with ER-negative disease than with ER-positive disease in *BRCA1* mutation carriers (per-allele ER-negative HR, 1.22; 95% CI, 1.14–1.30; $P = 4.4 \times 10^{-9}$; per-allele ER-positive HR, 1.14; 95% CI, 1.01–1.30; $P = 0.040$), the difference was not significant ($P = 0.41$; Table 3). rs67397200, however, was associated with ER-negative disease (per-allele HR, 1.29; 95% CI, 1.11–1.49; $P = 8.7 \times 10^{-4}$) but not ER-positive disease (per-allele HR, 0.92; 95% CI, 0.85–1.01; $P = 0.074$) in *BRCA2* mutation carriers ($P_{\text{heterogeneity}} = 1.5 \times 10^{-4}$; Table 3). The lack of association with rs311499 at 20q13.3 did not vary by ER status in *BRCA1* or *BRCA2* mutation carriers. For *BRCA2* mutation carriers, the minor allele of rs16917302 at *ZNF365* was inversely associated with both ER-positive (per-allele HR, 0.86; 95% CI, 0.75–0.97; $P = 0.016$) and ER-negative tumors (per-allele HR, 0.79; 95% CI, 0.62–1.00; $P = 0.048$; $P_{\text{heterogeneity}} = 0.56$; Table 3). However, in *BRCA1* mutation carriers, rs16917302 was associated with ER-positive (per-allele ER-positive HR, 0.77; 95% CI, 0.62–0.95; $P = 0.016$) but not ER-negative status ($P_{\text{heterogeneity}} = 0.028$; Table 3).

BRCA1 and *BRCA2* mutations are associated with elevated risk of ovarian cancer. In this CIMBA study, 1,465 *BRCA1* mutation carriers and 453 *BRCA2* mutation carriers who developed ovarian cancer were also genotyped for the 4 SNPs under study. To assess the influence of these SNPs on ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers, we used a competing risk analysis that evaluated the associations with breast and ovarian cancer risk simultaneously. While previous studies did not detect an association between rs8170 at 19p13.1 and ovarian cancer in *BRCA1* or *BRCA2* mutation carriers (5), in this

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Table 3. Associations between SNPs and breast cancer risk by ER status of breast cancer cases among women with *BRCA1* and *BRCA2* mutations

		Affected[a] (N)		ER$^+$		ER$^-$		Case P_{het}[b]
SNP/mutation	Unaffected, N	ER$^-$	ER$^+$	HR (95% CI)	P_{trend}	HR (95% CI)	P_{trend}	P_{trend}
rs8170—19p13.1								
BRCA1	4,483	1,820	541	1.12 (0.96–1.29)	0.15	1.23 (1.14–1.33)	2.0×10^{-7}	0.26
BRCA2	2,738	401	1,343	0.94 (0.85–1.05)	0.26	1.18 (0.99–1.40)	0.058	0.026
rs67397200—19p13.1								
BRCA1	4,486	1,821	542	1.14 (1.01–1.30)	0.040	1.22 (1.14–1.30)	4.4×10^{-9}	0.41
BRCA2	2,733	401	1,349	0.92 (0.85–1.01)	0.074	1.29 (1.11–1.49)	8.7×10^{-4}	1.5×10^{-4}
rs311499—20q13.3								
BRCA1	4,898	1,890	559	1.07 (0.87–1.31)	0.51	0.95 (0.85–1.06)	0.35	0.31
BRCA2	2,930	406	1,372	0.95 (0.82–1.09)	0.48	0.83 (0.63–1.10)	0.19	0.40
rs16917302-–10q21.2								
BRCA1	4,897	1,888	558	0.77 (0.62–0.95)	0.016	1.01 (0.92–1.11)	0.85	0.028
BRCA2	2,927	406	1,372	0.86 (0.75–0.97)	0.016	0.79 (0.62–1.00)	0.048	0.56

[a]Breast cancer

[b]*P* value for heterogeneity in the associations with ER-positive and ER-negative breast cancer.

competing risk analysis with larger numbers of *BRCA1* and *BRCA2* mutation carriers, rs8170 was significantly associated with ovarian cancer risk in both *BRCA1* (HR, 1.15; 95% CI, 1.03–1.29; $P = 0.015$) and *BRCA2* (HR, 1.34; 95% CI, 1.12–1.62; $P = 1.9 \times 10^{-3}$) mutation carriers (Table 4). Similarly rs67397200 at 19p13.1 was associated with ovarian cancer risk in both *BRCA1* (HR, 1.16; 95% CI, 1.05–1.29; $P = 3.8 \times 10^{-4}$) and *BRCA2* (HR, 1.30; 95% CI, 1.10–1.52; $P = 1.8 \times 10^{-3}$) mutation carriers (Table 4). rs311499 at 20q13.3 and rs16917302 at *ZNF365* were not associated with ovarian cancer risk for either *BRCA1* or *BRCA2* mutation carriers (Table 4).

Discussion

GWAS of *BRCA1* and *BRCA2* mutation carriers previously identified variants at 19p13.1, *ZNF365*, and 20q13.3 as candidate breast cancer risk modifiers (5, 7). In this study, we further evaluated associations between variants at these loci and both breast and ovarian cancer in *BRCA1* and *BRCA2* mutation carriers. For the first time, we found that both rs8170 and the previously imputed rs67397200 at 19p13.1 were strongly associated with ovarian cancer in both *BRCA1* and *BRCA2* mutation carriers. In addition, we found that rs8170 and rs67397200 at 19p13.1 were associated with breast cancer risk for *BRCA1* and rs16917302 at *ZNF365* was associated with breast cancer in *BRCA2* mutation carriers in this replication study using an independent set of mutation carriers and in the combined analyses of data from the original study and the replication study. In contrast, rs311499 at 20q13.3 showed no association with breast cancer in the replication study. We also report for the first time that the *BRCA1* GWAS SNP rs67397200 is associated with ER-negative breast cancer in *BRCA2* mutation carriers and that the *BRCA2* GWAS SNP rs16917302 is associated with ER-positive disease in *BRCA1* mutation carriers.

The GWAS for breast cancer in *BRCA1* mutation carriers originally identified significant associations between variants at the 19p13.1 locus and risk of breast cancer. Five SNPs including rs8170 from a 39-kb region were associated with risk of disease. In an analysis of joint effects of these SNPs on breast cancer risk, the best model included rs8170 or rs4808611 and rs8100241 or rs2363956 (P for inclusion $= 7.7 \times 10^{-5}$ and $P = 6.7 \times 10^{-5}$ for rs8170 and rs8100241, respectively; ref. 5), suggesting that the associations were driven by a single causative variant partially correlated with all 5 SNPs. Imputation of additional SNPs in the region from the 1000 Genome Project identified 8 perfectly correlated SNPs within a 13-kb region that were more significantly associated with breast cancer risk. Of these, we chose rs67397200, which has an $r^2 = 0.58$ with rs8170 and $r^2 = 0.37$ with rs8100241/rs2363956, for further genotyping in an effort to determine whether this SNP (or 1 of the 7 other highly correlated SNPs) exhibited stronger associations with breast cancer. In an analysis of rs8170 in 11,669 and rs67397200 in 10,312 *BRCA1* mutation carriers, we observed similarly strong associations with breast cancer for *BRCA1* mutation carriers. In a joint analysis of rs8170 and rs67397200, allowing for haplotype structure, only rs67397200 remained significant. We were unable to genotype some of the original GWAS SNPs (rs2363956/rs8100241) in the present study and, as a consequence, could not evaluate the joint associations with rs67397200. It is therefore still unclear whether rs67397200 accounts solely for the association signal. The 35-kb region containing rs8170 and rs67397200 includes the *ABHD8*

Table 4. Associations with SNPs and breast and ovarian cancer risk using a competing risk analysis model among *BRCA1* and *BRCA2* mutation carriers of European ancestry

					Breast cancer		Ovarian cancer	
SNP/mutation	Genotype	Unaffected, N (%)	Breast cancer, N (%)	Ovarian cancer,N (%)	HR (95% CI)	*P*	HR (95% CI)	*P*
rs8170—19p13.1								
BRCA1	GG	2,972 (67.9)	3,730 (63.3)	923 (66.0)	1.00		1.00	
	AG	1,269 (29.0)	1,936 (32.9)	434 (31.0)	1.26 (1.17–1.36)		1.23 (1.08–1.42)	
	AA	139 (3.2)	224 (3.8)	42 (3.0)	1.34 (1.10–1.63)		1.04 (0.72–1.50)	
	Per-allele				1.22 (1.14–1.30)	2.1×10^{-9}	1.15 (1.03–1.29)	0.015
BRCA2	GG	1,788 (67.0)	2,494 (68.2)	266 (62.2)	1.00		1.00	
	AG	796 (29.9)	1,024 (28.0)	137 (32.0)	0.95 (0.85–1.05)		1.17 (0.93–1.47)	
	AA	83 (3.1)	138 (3.8)	25 (5.8)	1.37 (1.05–1.80)		2.72 (1.65–4.48)	
	Per-allele				1.02 (0.94–1.12)	0.62	1.34 (1.12–1.62)	1.9×10^{-3}
rs67397200—19p13.1								
BRCA1	CC	1,903 (51.5)	2,436 (46.0)	652 (49.7)	1.00		1.00	
	GC	1,498 (40.5)	2,381 (44.9)	540 (41.2)	1.28 (1.18–1.38)		1.16 (1.01–1.33)	
	GG	298 (8.1)	484 (9.1)	120 (9.2)	1.33 (1.16–1.53)		1.36 (1.07–1.73)	
	Per-allele				1.20 (1.13–1.27)	4.5×10^{-10}	1.16 (1.05–1.29)	3.8×10^{-4}
BRCA2	CC	1,363 (50.5)	1,866 (50.7)	194 (45.2)	1.00		1.00	
	GC	1,123 (41.6)	1,489 (40.5)	184 (42.9)	0.96 (0.87–1.06)		1.15 (0.92–1.44)	
	GG	214 (7.9)	323 (8.8)	51 (11.9)	1.18 (0.99–1.41)		1.95 (1.37–2.77)	
	Per-allele				1.03 (0.96–1.11)	0.39	1.30 (1.10–1.52)	1.8×10^{-3}
rs311499—20q13.3								
BRCA1	GG	4,115 (86.0)	5,442 (85.9)	1,273 (86.9)	1.00		1.00	
	AG	637 (13.3)	869 (13.7)	183 (12.5)	1.01 (0.92–1.12)		0.88 (0.74–1.05)	
	AA	32 (0.7)	28 (0.4)	9 (0.6)	0.70 (0.42–1.17)		1.16 (0.47–2.87)	
	Per-allele				0.99 (0.90–1.08)	0.77	0.91 (0.77–1.07)	0.25
BRCA2	GG	2,492 (86.7)	3,303 (87.0)	390 (86.1)	1.00		1.00	
	AG	372 (12.9)	474 (12.5)	58 (12.8)	0.93 (0.82–1.07)		0.92 (0.68–1.26)	
	AA	11 (0.4)	21 (0.6)	5 (1.1)	1.09 (0.68–1.74)		2.23 (0.80–6.22)	
	Per-allele				0.95 (0.84–1.08)	0.44	1.02 (0.76–1.37)	0.88
rs16917302—10q21.2								
BRCA1	AA	3,784 (79.2)	5,044 (79.7)	1,169 (79.8)	1.00		1.00	
	CA	937 (19.6)	1,216 (19.2)	285 (19.5)	0.96 (0.88–1.04)		0.97 (0.84–1.13)	
	CC	60 (1.3)	73 (1.2)	11 (0.8)	0.86 (0.62–1.19)		0.47 (0.25–0.92)	
	Per-allele				0.95 (0.88–1.03)	0.21	0.92 (0.80–1.05)	0.20
BRCA2	AA	2,237 (77.9)	3,094 (81.5)	353 (78.1)	1.00		1.00	
	CA	601 (20.9)	671 (17.7)	93 (20.6)	0.81 (0.72–0.92)		0.93 (0.72–1.21)	
	CC	35 (1.2)	32 (0.8)	6 (1.3)	0.80 (0.50–1.30)		1.21 (0.46–3.18)	
	Per-allele				0.83 (0.74–0.92)	5.8×10^{-4}	0.96 (0.76–1.22)	0.76

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(abhydrolase domain containing 8), *ANKLE1* (ankyrin repeat and LEM domain containing 1), and *C19orf62* genes. *C19orf62*, encodes MERIT40 (mediator of Rap80 interactions and targeting 40 kD), a BRCA1-interacting protein that forms a complex with BRCA1–BARD1, Abraxas1, RAP80, BRCC36, and BRCC45 and is required for recruitment and retention of the BRCA1–BARD1 ubiquitin ligase at sites of DNA damage (15). Because alterations in MERIT40 expression or function may modify BRCA1 activity, variants in the *C19orf62* locus are attractive candidate breast cancer risk modifiers. However, as rs67397200 and the 7 other imputed SNPs that showed the most significant associations with breast cancer risk in *BRCA1* mutation carriers, are located at the 3′ end of *ANKLE1* near *ABHD8*, it is also possible that one of these genes rather than *C19orf62* is influenced by the underlying causative variants in this region. Further comprehensive genotyping of other common variants and/or rare SNPs from this locus and detailed functional studies will be required to resolve this issue.

Our GWAS for breast cancer in *BRCA2* mutation carriers previously identified strong associations between rs16917302 in the *ZNF365* (dbGENE ID: 22891) locus and breast cancer (7). We have now replicated this association for *BRCA2* mutation carriers. rs16917302 is located within intron 4 of *ZNF365* and is unique to isoform C, the longest of the 4 isoforms created by alternative splicing sites (16). In independent studies, rs10995195 in *ZNF365*, which is 27 kb upstream from and only weakly correlated ($r^2 = 0.1$) with rs16917302, has been associated with breast cancer risk (8) and with mammographic density (17) in the general population. In addition, a cluster of SNPs located 154 kb from rs16917302 in isoform D of *ZNF365* has been associated with Crohn disease (18–20), and the region has also been implicated in family-based linkage analyses with uric acid nephrolithiasis (21) and hypotrichosis (22). It is unclear whether there is genetic or biologic linkage between these seemingly disparate phenotypes. Further fine mapping of the *ZNF365* region and functional analyses will be needed to identify the causative variants for each phenotype and to understand the downstream biologic effects.

Likewise, rs311499 at 20q13.3 was associated with breast cancer risk in *BRCA2* mutation carriers in the *BRCA2* GWAS (per-allele HR, 0.72; 95% CI, 0.61–0.85; $P = 6.6 \times 10^{-5}$). However, this association was not confirmed in the replication study described above (HR, 1.11; 95% CI, 0.94–1.31; $P = 0.22$) or in the combined analysis of the discovery and replication stages (HR, 0.95; 95% CI, 0.84–1.07; $P = 0.36$). This result was not unexpected because the association between rs311499 and breast cancer did not reach significance ($P < 0.05$) in stage II of the *BRCA2* GWAS (HR, 0.86; 95% CI, 0.67–1.06; $P = 0.13$; ref. 7).

To further characterize the influence of the 19p13.1 and *ZNF365* loci on breast cancer risk, we assessed the strength of association with ER-negative and ER-positive breast cancer in *BRCA1* and *BRCA2* mutation carriers. As reported above, rs67397200 at 19p13.1 was associated with both ER-negative and ER-positive breast cancer in *BRCA1* mutation carriers, whereas rs8170 at 19p13.1 was only associated with ER-negative disease. Interestingly, rs67397200 and rs8170 were also associated with ER-negative breast cancer but not ER-positive breast cancer in *BRCA2* mutation carriers. This is consistent with our previous finding that rs8170 at 19p13.1 is more strongly associated with ER-negative than ER-positive breast cancer in the general population (5). Given that the majority of *BRCA1* breast tumors exhibit a basal breast cancer phenotype (14), it remains to be determined whether ER-positive basal cases account for the mild association with ER-positive disease in *BRCA1* mutation carriers.

In contrast, we found that rs16917302 in the *ZNF365* locus was associated with both ER-positive and ER-negative disease in *BRCA2* mutation carriers. This was consistent with associations for both ER-positive and ER-negative breast cancer in a recent GWAS of breast cancer cases with a family history of the disease (8). In contrast, among *BRCA1* mutation carriers, the association with breast cancer risk was restricted to ER-positive cases. This suggests that refinement of phenotype, perhaps in specific subpopulations, may result in detection of previously hidden associations.

Ovarian cancer is an important component of the cancer phenotype in both *BRCA1* and *BRCA2* mutation carriers. Because breast and ovarian cancer can occur in the same mutation carriers, it has been suggested that susceptibility SNPs common to breast and ovarian cancer may exist in these populations. However, to date, none of the SNPs associated with breast cancer risk in *BRCA1* or *BRCA2* mutation carriers have been associated with ovarian cancer risk. Similarly, SNPs in the *BCN2* locus that are associated with ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers are not associated with breast cancer risk (13). Furthermore, in the general population, only SNPs in the 8q24 locus are known to influence both breast and ovarian cancer, and these appear to be independent disease-specific effects (23). Thus, the recent finding that SNPs at 19p13.1 were associated with breast cancer in *BRCA1* mutation carriers (5) and also with ovarian cancer in the general population (6) raised the possibility that a locus with common influences on breast and ovarian cancer does exist. However, the *BRCA1* GWAS failed to detect any association for 19p13.1 SNPs with ovarian cancer among *BRCA1* mutation carriers (843 ovarian cases; HR, 1.07; 95% CI, 0.93–1.24; $P = 0.33$; ref. 5). Here, we reevaluated associations between 19p13.1 SNPs and ovarian cancer using larger numbers of *BRCA1* ($n = 1{,}312$) and *BRCA2* ($n = 429$) carriers diagnosed with ovarian cancer. rs67397200 at 19p13.1 was associated with ovarian cancer risk in both *BRCA1* (HR, 1.16; 95% CI, 1.05–1.29; $P = 3.8 \times 10^{-4}$) and *BRCA2* (HR, 1.30; 95% CI, 1.10–1.52; $P = 1.8 \times 10^{-3}$) mutation carriers. The magnitude of the effect on ovarian cancer risk in *BRCA1* carriers (HR = 1.16) was similar to that observed for breast cancer. This is

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the first locus found to influence both breast and ovarian cancer risk in either *BRCA1* or *BRCA2* mutation carriers.

Including the SNPs from the present study, 6 loci are now known to modify the risk of breast cancer for *BRCA1* mutation carriers [*CASP8*, *TOX3*, 2q35, 6q25.1, 19p13, and *ZNF365* (ER-positive disease only); refs. 1–3, 5, 10, 24] and 10 loci are known to modify the risk of breast cancer for *BRCA2* mutation carriers [*FGFR2*, *TOX3*, *MAP3K1*, *LSP1*, 2q35, *SLC4A7*, 5p12, *ZNF365*, 1p11.2, and 19p13.1 (ER-negative only); refs. 5, 7, 10, 24]. Taken together, these SNPs result in large variation in the absolute risk of breast cancer for *BRCA1* and *BRCA2* mutation carriers and may further improve our ability to provide individualized risks of breast cancer for *BRCA1* and *BRCA2* mutation carriers.

Disclosure of Potential Conflicts of Interest

The Editor-in-Chief of *Cancer Epidemiology, Biomarkers & Prevention* is an author of this article. In keeping with the AACR's Editorial Policy, the manuscript was peer reviewed and a member of the AACR's Publications Committee rendered the decision concerning acceptability. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the BCFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government or the BCFR. No potential conflicts of interest are disclosed.

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Genome-Wide Association Study in *BRCA1* Mutation Carriers Identifies Novel Loci Associated with Breast and Ovarian Cancer Risk

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Abstract

BRCA1-associated breast and ovarian cancer risks can be modified by common genetic variants. To identify further cancer risk-modifying loci, we performed a multi-stage GWAS of 11,705 *BRCA1* carriers (of whom 5,920 were diagnosed with breast and 1,839 were diagnosed with ovarian cancer), with a further replication in an additional sample of 2,646 *BRCA1* carriers. We identified a novel breast cancer risk modifier locus at 1q32 for *BRCA1* carriers (rs2290854, $P = 2.7 \times 10^{-8}$, HR = 1.14, 95% CI: 1.09–1.20). In addition, we identified two novel ovarian cancer risk modifier loci: 17q21.31 (rs17631303, $P = 1.4 \times 10^{-8}$, HR = 1.27, 95% CI: 1.17–1.38) and 4q32.3 (rs4691139, $P = 3.4 \times 10^{-8}$, HR = 1.20, 95% CI: 1.17–1.38). The 4q32.3 locus was not associated with ovarian cancer risk in the general population or *BRCA2* carriers, suggesting a *BRCA1*-specific association. The 17q21.31 locus was also associated with ovarian cancer risk in 8,211 *BRCA2* carriers ($P = 2 \times 10^{-4}$). These loci may lead to an improved understanding of the etiology of breast and ovarian tumors in *BRCA1* carriers. Based on the joint distribution of the known *BRCA1* breast cancer risk-modifying loci, we estimated that the breast cancer lifetime risks for the 5% of *BRCA1* carriers at lowest risk are 28%–50% compared to 81%–100% for the 5% at highest risk. Similarly, based on the known ovarian cancer risk-modifying loci, the 5% of *BRCA1* carriers at lowest risk have an estimated lifetime risk of developing ovarian cancer of 28% or lower, whereas the 5% at highest risk will have a risk of 63% or higher. Such differences in risk may have important implications for risk prediction and clinical management for *BRCA1* carriers.

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Introduction

Breast and ovarian cancer risk estimates for *BRCA1* mutation carriers vary by the degree of family history of the disease, suggesting that other genetic factors modify cancer risks for this population [1–4]. Studies by the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) have shown that a subset of common alleles influencing breast and ovarian cancer risk in the general population are also associated with cancer risk in *BRCA1* mutation carriers [5–11]. In particular, the breast cancer associations were limited to loci associated with estrogen receptor (ER)-negative breast cancer in the general population (6q25.1, 12p11 and *TOX3*) [8–11].

To systematically search for loci associated with breast or ovarian cancer risk for *BRCA1* carriers we previously conducted a two-stage genome-wide association study (GWAS) [12]. The initial stage involved analysis of 555,616 SNPs in 2383 *BRCA1* mutation carriers (1,193 unaffected and 1,190 affected). After replication testing of 89 SNPs showing the strongest association, with 5,986 *BRCA1* mutation carriers, a locus on 19p13 was shown to be associated with breast cancer risk for *BRCA1* mutation carriers. The same locus was also associated with the risk of estrogen-receptor (ER) negative and triple negative (ER, Progesterone and HER2 negative) breast cancer in the general population [12,13].

The Collaborative Oncological Gene-environment Study (COGS) consortium recently developed a 211,155 SNP custom genotyping array (iCOGS) in order to provide cost-effective genotyping of common and rare genetic variants to identify novel loci that explain the residual genetic variance of breast, ovarian

Author Summary

BRCA1 mutation carriers have increased and variable risks of breast and ovarian cancer. To identify modifiers of breast and ovarian cancer risk in this population, a multi-stage GWAS of 14,351 *BRCA1* mutation carriers was performed. Loci 1q32 and *TCF7L2* at 10q25.3 were associated with breast cancer risk, and two loci at 4q32.2 and 17q21.31 were associated with ovarian cancer risk. The 4q32.3 ovarian cancer locus was not associated with ovarian cancer risk in the general population or in *BRCA2* carriers and is the first indication of a *BRCA1*-specific risk locus for either breast or ovarian cancer. Furthermore, modeling the influence of these modifiers on cumulative risk of breast and ovarian cancer in *BRCA1* mutation carriers for the first time showed that a wide range of individual absolute risks of each cancer can be estimated. These differences suggest that genetic risk modifiers may be incorporated into the clinical management of *BRCA1* mutation carriers.

and prostate cancers and fine-map known susceptibility loci. A total of 32,557 SNPs on the iCOGS array were selected on the basis of the *BRCA1* GWAS for the purpose of identifying breast and ovarian cancer risk modifiers for *BRCA1* mutation carriers. Genotype data from the iCOGS array were obtained for 11,705 samples from *BRCA1* carriers and the 17 most promising SNPs were then genotyped in an additional 2,646 *BRCA1* carriers. In this manuscript we report on the novel risk modifier loci identified by this multi-stage GWAS. No study has previously shown how the absolute risks of breast and ovarian cancer for *BRCA1* mutation carriers vary by the combined effects of risk modifying loci. Here we use the results from this study, in combination with previously identified modifiers, to obtain absolute risks of developing breast and ovarian cancer for *BRCA1* mutation carriers based on the joint distribution of all known genetic risk modifiers.

Materials and Methods

Ethics statement

All carriers participated in clinical or research studies at the host institutions, approved by local ethics committees.

Study subjects

BRCA1 mutation carriers were recruited by 45 study centers in 25 countries through CIMBA. The majority were recruited through cancer genetics clinics, and enrolled into national or regional studies. The remainder were identified by population-based sampling or community recruitment. Eligibility for CIMBA association studies was restricted to female carriers of pathogenic *BRCA1* mutations age 18 years or older at recruitment. Information collected included year of birth, mutation description, self-reported ethnic ancestry, age at last follow-up, ages at breast or ovarian cancer diagnoses, and age at bilateral prophylactic mastectomy and oophorectomy. Information on tumour characteristics, including ER-status of the breast cancers, was also collected. Related individuals were identified through a unique family identifier. Women were included in the analysis if they carried mutations that were pathogenic according to generally recognized criteria.

GWAS stage 1 samples. A total of 2,727 *BRCA1* mutation carriers were genotyped on the Illumina Infinium 610K array (Figure 1). Of these 1,426 diagnosed with a first breast cancer under age 40 were considered "affected" in the breast cancer association analysis and 683 diagnosed with an ovarian cancer at any time were considered as "affected" in the ovarian cancer analysis. "Unaffected" in both analyses were over age 35 (Table S1) [12].

Replication study samples. All eligible *BRCA1* carriers from CIMBA with sufficient DNA were genotyped, including those used in Stage 1. In total, 13,310 samples from 45 centers in 25 countries were genotyped using the iCOGS array (Table S2). Among the 13,310 samples, those that were genotyped in the GWAS stage 1 SNP selection stage are referred to as "stage 1" samples, and the remainder are "stage 2" samples. An additional 2,646 *BRCA1* samples "stage 3" were genotyped on an iPLEX Mass Array of 17 SNPs from 12 loci selected after an interim analysis of iCOGS array data and were available for analysis after quality control (QC) (Figure 1). Carriers of pathogenic mutations in *BRCA2* were drawn from a parallel GWAS of genetic modifiers for *BRCA2* mutation carriers. *BRCA2* mutation carriers were recruited from CIMBA through 47 studies which were largely the same as the studies that contributed to the *BRCA1* GWAS with similar eligibility criteria. Samples from *BRCA2* mutation carriers were also genotyped using the iCOGS array. Details of this experiment are described elsewhere [14]. A total of 8,211 samples were available for analysis after QC.

iCOGS SNP array

The iCOGS array was designed in a collaboration among the Breast Cancer Association Consortium (BCAC), Ovarian Cancer Association Consortium (OCAC), the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) and CIMBA. The general aims for designing the iCOGS array were to replicate findings from GWAS for identifying variants associated with breast, ovarian or prostate cancer (including subtypes and SNPs potentially associated with disease outcome), to facilitate fine-mapping of regions of interest, and to genotype "candidate" SNPs of interest within the consortia, including rarer variants. Each consortium was given a share of the array: nominally 25% of the SNPs each for BCAC, PRACTICAL and OCAC; 17.5% for CIMBA; and 7.5% for SNPs of common interest between the consortia. The final design comprised 220,123 SNPs, of which 211,155 were successfully manufactured. A total of 32,557 SNPs on the iCOGS array were selected based on 8 separate analyses of stage 1 of the CIMBA *BRCA1* GWAS that included 2,727 *BRCA1* mutation carriers [12]. After imputation for all SNPs in HapMap Phase II (CEU) a total of 2,568,349 (imputation $r^2>0.30$) were available for analysis. Markers were evaluated for associations with: (1) breast cancer; (2) ovarian cancer; (3) breast cancer restricted to Class 1 mutations (loss-of-function mutations expected to result in a reduced transcript or protein level due to nonsense-mediated RNA decay); (4) breast cancer restricted to Class 2 mutations (mutations likely to generate stable proteins with potential residual or dominant negative function); (5) breast cancer by tumor ER-status; (6) breast cancer restricted to *BRCA1* 185delAG mutation carriers; (7) breast cancer restricted to *BRCA1* 5382insC mutation carriers; and (8) breast cancer by contrasting the genotype distributions in *BRCA1* mutation carriers, against the distribution in population-based controls. Analyses (1) and (2) were based on both imputed and observed genotypes, whereas the rest were based on only the observed genotypes. SNPs were ranked according to the 1 d.f. score-test for trend P-value (described below) and selected for inclusion based on nominal proportions of 61.5%, 20%, 2.5%, 2.5%, 2.5%, 0.5%, 0.5% and 10.0% for analyses (1) to (8). SNP duplications were not allowed and SNPs with a pairwise $r^2\geq0.90$ with a higher-ranking SNP were only allowed (up to a maximum

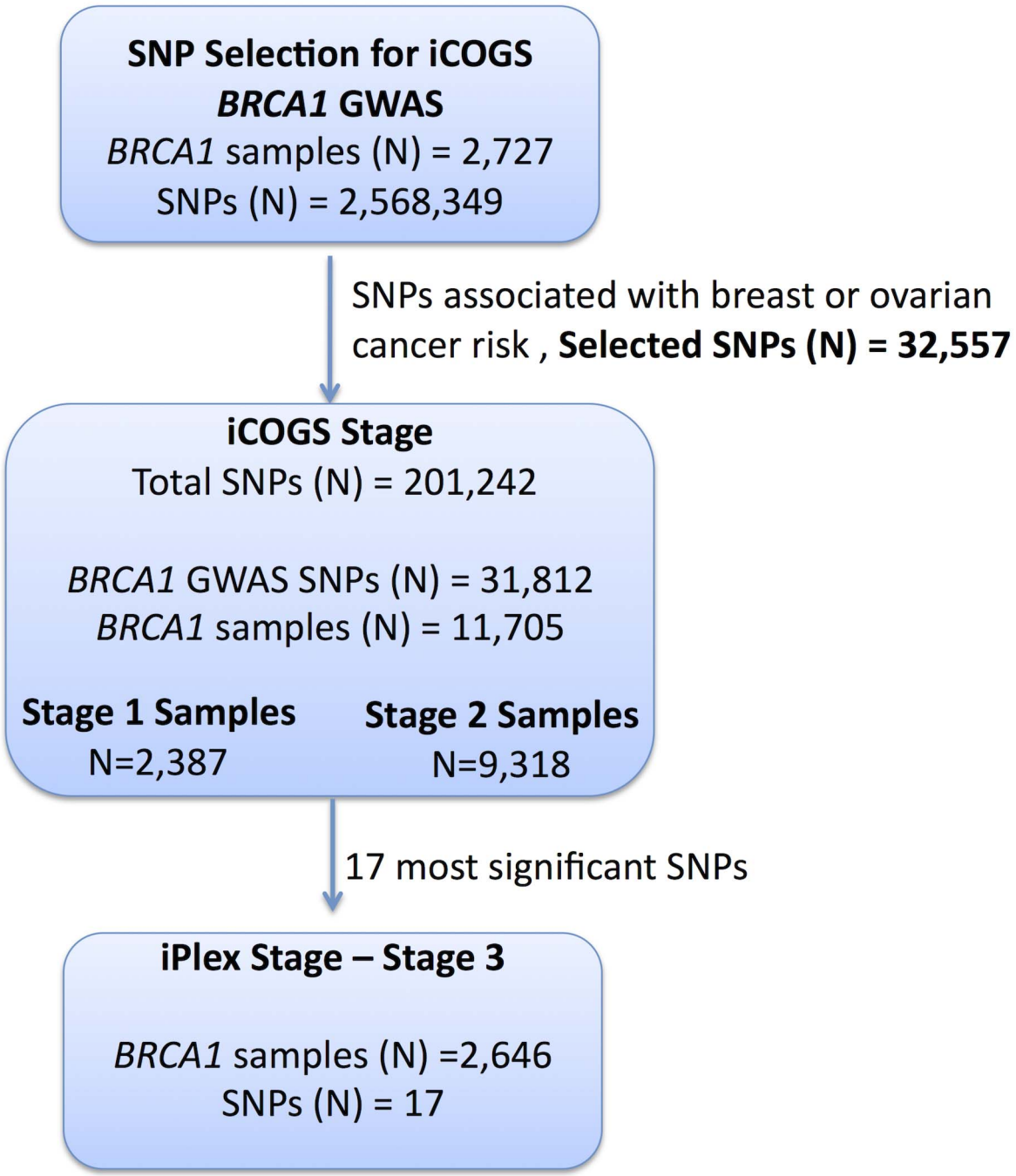

Figure 1. Study design for selection of the SNPs and genotyping of *BRCA1* samples. GWAS data from 2,727 *BRCA1* mutation carriers were analysed for associations with breast and ovarian cancer risk and 32,557 SNPs were selected for inclusion on the iCOGS array. A total of 11,705 *BRCA1* samples (after quality control (QC) checks) were genotyped on the 31,812 *BRCA1*-GWAS SNPs from the iCOGS array that passed QC. Of these samples, 2,387 had been genotyped at the SNP selection stage and are referred to as "stage 1" samples, whereas 9,318 samples were unique to the iCOGS study ("Stage 2" samples). Next, 17 SNPs that exhibited the most significant associations with breast and ovarian cancer were selected for genotyping in a third stage involving an additional 2,646 *BRCA1* samples (after QC).
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of 2) if the P-value for association was $<10^{-4}$ for analyses (1) and (2) and $<10^{-5}$ for other analyses. SNPs with poor Illumina design scores were replaced by the SNP with the highest r^2 (among SNPs with $r^2>0.80$ based on HapMap data) that had a good quality design score. The analysis of associations with breast and ovarian cancer risks presented here included all 32,557 SNPs on iCOGS that were selected on the basis of the *BRCA1* GWAS.

Genotyping and quality control

iCOGS genotyping. Genotyping was performed at Mayo Clinic. Genotypes for samples genotyped on the iCOGS array were called using Illumina's GenCall algorithm (Text S1). A total of 13,510 samples were genotyped for 211,155 SNPs. The sample and SNP QC process is summarised in Table S3. Of the 13,510 samples, 578 did not fulfil eligibility criteria based on phenotypic

data and were excluded. A step-wise QC process was applied to the remaining samples and SNPs. Samples were excluded due to inferred gender errors, low call rates (<95%), low or high heterozygosity and sample duplications (cryptic and intended). Of the 211,155 markers genotyped, 9,913 were excluded due to Y-chromosome origin, low call rates (<95%), monomorphic SNPs, or SNPs with Hardy-Weinberg equilibrium (HWE) $P<10^{-7}$ under a country-stratified test statistic [15] (Table S3). SNPs that gave discordant genotypes among known sample duplicates were also excluded. Multi-dimensional scaling was used to exclude individuals of non-European ancestry. We selected 37,149 weakly correlated autosomal SNPs (pair-wise $r^2<0.10$) to compute the genomic kinship between all pairs of *BRCA1* carriers, along with 197 HapMap samples (CHB, JPT, YRI and CEU). These were converted to distances and subjected to multidimensional scaling (Figure S1). Using the first two components, we calculated the proportion of European ancestry for each individual [12] and excluded samples with >22% non-European ancestry (Figure S1). A total of 11,705 samples and 201,242 SNPs were available for analysis, including 31,812 SNPs selected by the *BRCA1* GWAS. The genotyping cluster plots for all SNPs that demonstrated genome-wide significance level of association or are presented below, were checked manually for quality (Figure S2).

iPLEX analysis. The most significant SNPs from 4 loci associated with ovarian cancer and 8 loci associated with breast cancer were selected (17 SNPs in total) for stage 3 genotyping. Genotyping using the iPLEX Mass Array platform was performed at Mayo Clinic. CIMBA QC procedures were applied. Samples that failed for ≥20% of the SNPs were excluded from the analysis. No SNPs failed HWE ($P<0.01$). The concordance among duplicates was ≥98%. Mutation carriers of self-reported non-European ancestry were excluded. A total of 2,646 *BRCA1* samples were eligible for analysis after QC.

Statistical methods

The main analyses were focused on the evaluation of associations between each genotype and breast cancer or ovarian cancer risk separately. Analyses were carried out within a survival analysis framework. In the breast cancer analysis, the phenotype of each individual was defined by age at breast cancer diagnosis or age at last follow-up. Individuals were followed until the age of the first breast cancer diagnosis, ovarian cancer diagnosis, or bilateral prophylactic mastectomy, whichever occurred first; or last observation age. Mutation carriers censored at ovarian cancer diagnosis were considered unaffected. For the ovarian cancer analysis, the primary endpoint was the age at ovarian cancer diagnosis. Mutation carriers were followed until the age of ovarian cancer diagnosis, or risk-reducing salpingo-oophorectomy (RRSO) or age at last observation. In order to maximize the number of ovarian cancer cases, breast cancer was not considered as a censoring event in this analysis, and mutation carriers who developed ovarian cancer after a breast cancer diagnosis were considered as affected in the ovarian cancer analysis.

Association analysis. The majority of mutation carriers were sampled through families seen in genetic clinics. The first tested individual in a family is usually someone diagnosed with cancer at a relatively young age. Such study designs tend to lead to an over-sampling of affected individuals, and standard analytical methods like Cox regression may lead to biased estimates of the risk ratios [16,17]. To adjust for this potential bias the data were analyzed within a survival analysis framework, by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes. A detailed description of the retrospective likelihood approach has been published [17,18]. The associations between genotype and breast cancer risk at both stages were assessed using the 1 d.f. score test statistic based on this retrospective likelihood [17,18]. To allow for the non-independence among related individuals, we accounted for the correlation between the genotypes by estimating the kinship coefficient for each pair of individuals using the available genomic data [16,19,20] and by robust variance estimation based on reported family membership [21]. We chose to present P-values based on the kinship adjusted score test as it utilises the degree of relationship between individuals. A genome-wide level of significance of 5×10^{-8} was used [22]. These analyses were performed in R using the GenABEL [23] libraries and custom-written functions in FORTRAN and Python.

To estimate the magnitude of the associations (HRs), the effect of each SNP was modeled either as a per-allele HR (multiplicative model) or as genotype-specific HRs, and were estimated on the log-scale by maximizing the retrospective likelihood. The retrospective likelihood was fitted using the pedigree-analysis software MENDEL [17,24]. As sample sizes varied substantially between contributing centers heterogeneity was examined at the country level. All analyses were stratified by country of residence and used calendar-year and cohort-specific breast cancer incidence rates for *BRCA1* [25]. Countries with small number of mutation carriers were combined with neighbouring countries to ensure sufficiently large numbers within each stratum (Table S2). USA and Canada were further stratified by reported Ashkenazi Jewish (AJ) ancestry due to large numbers of AJ carriers. In stage 3 analysis involving several countries with small numbers of mutation carriers, we assumed only 3 large strata (Europe, Australia, USA/Canada). The combined iCOGS stage and stage 3 analysis was also stratified by stage of the experiment. The analysis of associations by breast cancer ER-status was carried out by an extension of the retrospective likelihood approach to model the simultaneous effect of each SNP on more than one tumor subtype [26] (Text S1).

Competing risk analysis. The associations with breast and ovarian cancer risk simultaneously were assessed within a competing risk analysis framework [17] by estimating HRs simultaneously for breast and ovarian cancer risk. This analysis provides unbiased estimates of association with both diseases and more powerful tests of association in cases where an association exists between a variant and at least one of the diseases [17]. Each individual was assumed to be at risk of developing either breast or ovarian cancer, and the probabilities of developing each disease were assumed to be independent conditional on the underlying genotype. A different censoring process was used, whereby individuals were followed up to the age of the first breast or ovarian cancer diagnosis and were considered to have developed the corresponding disease. No follow-up was considered after the first cancer diagnosis. Individuals censored for breast cancer at the age of bilateral prophylactic mastectomy and for ovarian cancer at the age of RRSO were assumed to be unaffected for the corresponding disease. The remaining individuals were censored at the last observation age and were assumed to be unaffected for both diseases.

Imputation. For the SNP selection process, the MACH software was used to impute non-genotyped SNPs based on the phased haplotypes from HapMap Phase II (CEU, release 22). The IMPUTE2 software [27] was used to impute non-genotyped SNPs for samples genotyped on the iCOGS array (stage 1 and 2 only), based on the 1,000 Genomes haplotypes (January 2012 version). Associations between each marker and cancer risk were assessed using a similar score test to that used for the observed SNPs, but based on the posterior genotype probabilities at each imputed marker for each individual. In all analyses, we considered only SNPs with imputation information/accuracy $r^2>0.30$.

Absolute breast and ovarian cancer risks by combined SNP profile. We estimated the absolute risk of developing breast and ovarian cancer based on the joint distribution of all SNPs that were significantly associated with risk for *BRCA1* mutation carriers based on methods previously applied to *BRCA2* carriers [28]. We assumed that the average, age-specific breast and ovarian cancer incidences for *BRCA1* mutation carriers, over all modifying loci, agreed with published penetrance estimates for *BRCA1* [25]. The model assumed independence among the modifying loci and we used only the SNP with the strongest evidence of association from each region. We used only loci identified through the *BRCA1* GWAS that exhibited associations at a genome-wide significance level, and loci that were identified through population-based GWAS of breast or ovarian cancer risk, but were also associated with those risks for *BRCA1* mutation carriers. For each SNP, we used the per-allele HR and minor allele frequencies estimated from the present study. Genotype frequencies were obtained under the assumption of HWE.

Results

Samples from 11,705 *BRCA1* carriers from 45 centers in 25 countries yielded high-quality data for 201,242 SNPs on the iCOGS array. The array included 31,812 *BRCA1* GWAS SNPs, which were analyzed here for their associations with breast and ovarian cancer risk for *BRCA1* mutation carriers (Table S2). Of the 11,705 *BRCA1* mutation carriers, 2,387 samples had also been genotyped for stage 1 of the GWAS and 9,318 were unique to the stage 2 iCOGS study.

Breast cancer associations

When restricting analysis to stage 2 samples (4,681 unaffected, 4,637 affected), there was little evidence of inflation in the association test-statistic ($\lambda = 1.038$; Figure S3). Combined analysis of stage 1 and 2 samples (5,784 unaffected, 5,920 affected) revealed 66 SNPs in 28 regions with $P<10^{-4}$ (Figure S4). These included variants from three loci (19p13, 6q25.1, 12p11) previously associated with breast cancer risk for *BRCA1* mutation carriers (Table 1). Further evaluation of 18 loci associated with breast cancer susceptibility in the general population found that only the *TOX3*, *LSP1*, 2q35 and *RAD51L1* loci were significantly associated with breast cancer for *BRCA1* carriers (Table 1, Table S4).

After excluding SNPs from the known loci, there were 39 SNPs in 25 regions with $P = 1.2\times10^{-6}$–1.0×10^{-4}. Twelve of these SNPs were genotyped by iPLEX in an additional 2,646 *BRCA1* carriers (1,252 unaffected, 1,394 affected, "stage 3" samples, Table S5). There was additional evidence of association with breast cancer risk for four SNPs at two loci ($P<0.01$, Table 2). When all stages were combined, SNPs rs2290854 and rs6682208 ($r^2 = 0.84$) at 1q32, near *MDM4*, had combined *P*-values of association with breast cancer risk of 1.4×10^{-7} and 4×10^{-7},respectively. SNPs rs11196174 and rs11196175 ($r^2 = 0.96$) at 10q25.3 (in *TCF7L2*) had combined P-values of 7.5×10^{-7} and 1.2×10^{-6}. Analysis within a competing risks framework, where associations with breast and ovarian cancer risks are evaluated simultaneously [17], revealed stronger associations with breast cancer risk for all 4 SNPs, but no associations with ovarian cancer (Table 3). In particular, we observed a genome-wide significant association between the minor allele of rs2290854 from 1q32 and breast cancer risk (per-allele HR: 1.14; 95%CI: 1.09–1.20; $p = 2.7\times10^{-8}$). Country-specific HR estimates for all SNPs are shown in Figure S5. Analyses stratified by *BRCA1* mutation class revealed no significant evidence of a difference in the associations of any of the SNPs by the predicted functional consequences of *BRCA1* mutations (Table S6). SNPs in the *MDM4* and *TCF7L2* loci were associated with breast cancer risk for both class1 and class2 mutation carriers.

Both the 1q32 and 10q25.3 loci were primarily associated with ER-negative breast cancer for *BRCA1* (rs2290854: ER-negative HR = 1.16, 95%CI: 1.10–1.22, $P = 1.2\times10^{-7}$; rs11196174: HR = 1.14, 95%CI: 1.07–1.20, $P = 9.6\times10^{-6}$), although the differences between the ER-negative and ER-positive HRs were not significant (Table S7). Given that ER-negative breast cancers in *BRCA1* and *BRCA2* mutation carriers are phenotypically similar [29], we also evaluated associations between these SNPs and ER-negative breast cancer in 8,211 *BRCA2* mutation carriers. While the 10q25.3 SNPs were not associated with overall or ER-negative breast cancer risk for *BRCA2* carriers, the 1q32 SNPs were associated with ER-negative (rs2290854 HR = 1.16, 95%CI:1.01–1.34, P = 0.033; rs6682208 HR = 1.19, 95%CI:1.04–1.35, P = 0.016), but not ER-positive breast cancer (rs2290854 P-diff = 0.006; rs6682208 P-diff = 0.001). Combining the *BRCA1* and *BRCA2* samples provided strong evidence of association with ER-negative breast cancer (rs2290854: $P = 1.25\times10^{-8}$; rs6682208: $P = 2.5\times10^{-7}$).

The iCOGS array included additional SNPs from the 1q32 region that were not chosen based on the *BRCA1* GWAS. Of these non-*BRCA1* GWAS SNPs, only SNP rs4951407 was more significantly associated with risk than the *BRCA1*-GWAS selected SNPs ($P = 3.3\times10^{-6}$, HR = 1.12, 95%CI:1.07–1.18, using stage 1 and stage 2 samples). The evidence of association with breast cancer risk was again stronger under the competing risks analysis (HR = 1.14, 95%CI: 1.08–1.20, $P = 6.1\times10^{-7}$). Backward multiple regression analysis, considering only the genotyped SNPs ($P<0.01$), revealed that the most parsimonious model included only rs4951407. SNPs from the 1000 Genomes Project, were imputed for the stage 1 and stage 2 samples (Figure S6). Only imputed SNP rs12404974, located between *PIK3C2B* and *MDM4* ($r^2 = 0.77$ with rs4951407), was more significantly associated with breast cancer ($P = 2.7\times10^{-6}$) than any of the genotyped SNPs. None of the genotyped or imputed SNPs from 10q25.3 provided P-values smaller than those for rs11196174 and rs11196175 (Figure S7).

Ovarian cancer associations

Analyses of associations with ovarian cancer risk using the stage 2 samples (8,054 unaffected, 1,264 affected) revealed no evidence of inflation in the association test-statistic ($\lambda = 1.039$, Figure S3). In the combined analysis of stage 1 and 2 samples (9866 unaffected, 1839 affected), 62 SNPs in 17 regions were associated with ovarian cancer risk for *BRCA1* carriers at $P<10^{-4}$ (Figure S3). These included SNPs in the 9p22 and 3q25 loci previously associated with ovarian cancer risk in both the general population and *BRCA1* carriers [6,7] (Table 1). Associations ($P<0.01$) with ovarian cancer risk were also observed for SNPs in three other known ovarian cancer susceptibility loci (8q24, 17q21, 19p13), but not 2q31 (Table 1). For all loci except 9p22, SNPs were identified that displayed smaller P-values of association than previously published results [5–7].

After excluding SNPs from known ovarian cancer susceptibility regions, there were 48 SNPs in 15 regions with $P = 5\times10^{-7}$ to 10^{-4}. Five SNPs from four of these loci were genotyped in the stage 3 samples (2,204 unaffected, 442 with ovarian cancer). Three SNPs showed additional evidence of association with ovarian cancer risk ($P<0.02$, Table 2; Table S5). In the combined stage 1–3 analyses, SNPs rs17631303 and rs183211 ($r^2 = 0.68$) on chromosome 17q21.31 had P-values for association of 1×10^{-8} and 3×10^{-8} respectively, and rs4691139 at 4q32.3 had a P-value of 3.4×10^{-8} (Table 2).

The minor alleles of rs17631303 (HR = 1.27, 95%CI:1.17–1.38) and rs183211 (HR = 1.25, 95%CI: 1.16–1.35) at 17q21.31 were associated with increased ovarian cancer risk (Table 2). Analysis of

Table 1. Associations with breast or ovarian cancer risk for loci previously reported to be associated with cancer risk for *BRCA1* mutation carriers.

Locus	Previously published association in *BRCA1*				Strongest association in current set of 31,812 *BRCA1* GWAS SNPs					Association for published SNP in set of all iCOGS SNPs			
	SNP	all1/all2 (freq)	HR (95%CI)	P	SNP	all1/all2 (freq)	r^2	HR (95%CI)	P	Best tag SNP (r^2)	all1/all2 (freq)	HR (95%CI)	P
Loci previously associated with breast cancer risk for BRCA1 carriers													
19p13	rs8170	G/A (0.17)	1.26 (1.17–1.35)	2.3×10^{-9}	rs8100241	G/A (0.52)	0.31	0.84 (0.80–0.88)	4.3×10^{-13}	rs8170 (1.0)	G/A (0.17)	1.22 (1.14–1.29)	4.8×10^{-10}
6q25.1	rs2046210	C/T (0.35)	1.17 (1.11–1.23)	4.5×10^{-9}	rs3734805	A/C (0.08)	0.25	1.28 (1.18–1.39)	5×10^{-9}	rs2046210* (1.0)	G/A (0.35)	1.15 (1.10–1.21)	2.8×10^{-8}
12p11	rs10771399	A/G (0.11)	0.87 (0.81–0.94)	3.2×10^{-4}	rs7957915	A/G (0.14)	0.85	0.85 (0.79–0.91)	8.1×10^{-6}	rs10771399*	A/G (0.11)	0.85 (0.79–0.92)	2.7×10^{-5}
TOX3	rs3803662	C/T (0.29)	1.09 (1.03–1.16)	0.0049	rs4784220	A/G (0.38)	0.52	1.08 (1.03–1.13)	0.0021	rs3803662*	G/A (0.29)	1.05 (1.00–1.11)	0.075
2q35	rs13387042[a]	G/A (0.52)	1.02 (0.96–1.07)	0.57	rs13389571	A/G (0.05)	0.02	0.86 (0.77–0.96)	0.011	rs13387042*	A/G (0.48)	1.01 (0.96–1.06)	0.74
Known ovarian cancer susceptibility loci													
9p22	rs3814113	T/C (0.34)	0.78 (0.72–0.85)	4.8×10^{-9}	rs3814113	A/G (0.34)	1.00	0.77 (0.71–0.83)	5.9×10^{-11}	rs3814113 (1.0)	A/G (0.34)	0.77 (0.71–0.83)	5.9×10^{-11}
2q31	rs2072590	T/C (0.31)	1.06 (0.98–1.14)	0.16	rs1026032	A/G (0.26)	0.75	1.08 (0.99–1.17)	0.064	rs2072590* (1.0)	C/A (0.32)	1.05 (0.97–1.14)	0.20
8q24	rs10088218	G/A (0.13)	0.89 (0.81–0.99)	0.029	rs9918771	A/C (0.17)	0.31	0.86 (0.78–0.95)	0.0021	rs10088218 (1.0)	G/A (0.13)	0.86 (0.78–0.96)	0.0096
3q25	rs2665390	T/C (0.075)	1.25 (1.10–1.42)	2.7×10^{-3}	rs7651446	C/A (0.043)	0.71	1.46 (1.25–1.71)	6.6×10^{-6}	rs344008 (1.0)	G/A (0.075)	1.21 (1.07–1.38)	3.8×10^{-3}
17q21	rs9303542	T/C (0.26)	1.08 (1.00–1.17)	0.06	rs11651753	G/A (0.43)	0.36	1.14 (1.06–1.23)	4.6×10^{-4}	rs9303542* (1.0)	A/G (0.26)	1.12 (1.04–1.22)	8.0×10^{-3}
19p13[b]	rs67397200	C/G (0.28)	1.16 (1.05–1.29)	3.8×10^{-4}	c19_pos17158477	G/C (0.038)	0.01	0.64 (0.49–0.83)	7.0×10^{-4}	rs67397200 (c19_pos17262404)	G/C (0.28)	1.12 (1.01–1.23)	0.027

Freq = frequency of allele 2 in unaffected *BRCA1* carriers.
HR = Per allele Hazard Ratio associated with allele 2, under a single disease risk model, unless specified.
r^2: correlation between the SNP in the present study and the published SNP.
*SNP not in *BRCA1* GWAS SNP allocation on iCOGS chip.
[a]: rs13387042 was previously found to be associated only under the 2-df model.
[b]: analysis under a competing risks model.
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Table 2. Associations with breast and ovarian cancer risk for SNPs found to be associated with risk at all 3 stages of the experiment.

SNP, Chr, Position, Allele1/ Allele2	Stage	Number		Allele 2 Frequency		HR* (95% CI)			
		Unaffected	Affected	Unaffected	Affected	Per Allele	Heterozygote	Homozygote	P-trend
Breast Cancer									
rs2290854, 1q32, 202782648, G/A	Stage 1	1104	1283	0.30	0.34	1.19 (1.08–1.30)	1.28 (1.12–1.47)	1.31 (1.06–1.61)	4.2×10^{-4}
	Stage 2	4681	4637	0.31	0.33	1.09 (1.03–1.16)	1.10 (1.02–1.19)	1.18 (1.03–1.35)	0.003
	Stages1+2	5785	5920	0.31	0.33	1.12 (1.06–1.17)	1.15 (1.07–1.23)	1.21 (1.08–1.36)	1.7×10^{-5}
	Stage 3	1252	1393	0.30	0.33	1.19 (1.07–1.32)	1.24 (1.07–1.43)	1.36 (1.06–1.74)	0.0013
	Combined	7037	7313	0.31	0.33	1.13 (1.08–1.18)	1.16 (1.09–1.24)	1.24 (1.11–1.37)	1.4×10^{-7}
rs6682208, 1q32, 202832806, G/A	Stage 1	1104	1283	0.32	0.35	1.14 (1.04–1.25)	1.24 (1.09–1.42)	1.20 (0.98–1.47)	0.0070
	Stage 2	4681	4637	0.32	0.34	1.10 (1.04–1.17)	1.09 (1.01–1.19)	1.21 (1.06–1.38)	0.0014
	Stages1+2	5785	5920	0.32	0.34	1.11 (1.05–1.17)	1.13 (1.05–1.21)	1.21 (1.08–1.35)	5.4×10^{-5}
	Stage 3	1250	1394	0.30	0.34	1.19 (1.07–1.32)	1.31 (1.14–1.51)	1.28 (1.01–1.63)	8.6×10^{-4}
	Combined	7035	7314	0.32	0.34	1.12 (1.07–1.17)	1.16 (1.09–1.23)	1.22 (1.11–1.35)	4.3×10^{-7}
rs11196174, 10q25.3, 114724086, A/G	Stage 1	1103	1282	0.27	0.32	1.15 (1.05–1.27)	1.17 (1.03–1.34)	1.31 (1.05–1.63)	0.0038
	Stage 2	4681	4636	0.29	0.31	1.10 (1.04–1.17)	1.13 (1.04–1.23)	1.17 (1.01–1.35)	0.0017
	Stages1+2	5784	5918	0.28	0.31	1.12 (1.06–1.18)	1.14 (1.06–1.23)	1.21 (1.07–1.37)	3.1×10^{-5}
	Stage 3	1251	1393	0.28	0.31	1.16 (1.05–1.29)	1.08 (0.93–1.25)	1.46 (1.15–1.85)	0.0057
	Combined	7035	7311	0.28	0.31	1.13 (1.07–1.18)	1.13 (1.06–1.21)	1.26 (1.13–1.40)	7.5×10^{-7}
rs11196175, 10q25.3, 114726604, A/G	Stage 1	1101	1280	0.27	0.31	1.15 (1.05–1.27)	1.18 (1.03–1.35)	1.29 (1.03–1.62)	0.0043
	Stage 2	4674	4627	0.28	0.30	1.10 (1.03–1.17)	1.13 (1.04–1.22)	1.17 (1.01–1.35)	0.0020
	Stages1+2	5775	5907	0.28	0.30	1.12 (1.06–1.18)	1.14 (1.06–1.22)	1.21 (1.07–1.37)	3.9×10^{-5}
	Stage 3	1251	1394	0.27	0.31	1.16 (1.04–1.29)	1.06 (0.91–1.22)	1.48 (1.17–1.87)	0.0075
	Combined	7026	7301	0.28	0.31	1.12 (1.07–1.18)	1.12 (1.05–1.20)	1.26 (1.13–1.41)	1.2×10^{-6}
Ovarian Cancer									
rs17631303, 17q21, 40872185, A/G	Stage 1	1797	574	0.19	0.25	1.46 (1.22–1.74)	1.36 (1.01–1.68)	2.46 (1.53–3.96)	1.3×10^{-5}
	Stage 2	7996	1257	0.19	0.21	1.20 (1.07–1.35)	1.10 (0.96–1.26)	1.83 (1.34–2.48)	1.5×10^{-3}
	Stages1+2	9793	1831	0.19	0.22	1.27 (1.16–1.40)	1.15 (1.03–1.29)	2.03 (1.16–2.61)	3.0×10^{-7}
	Stage 3	2204	442	0.17	0.21	1.27 (1.07–1.51)	1.24 (0.99–1.56)	1.67 (1.07–2.62)	0.014
	Combined	11997	2273	0.19	0.22	1.27 (1.17–1.38)	1.17 (1.06–1.29)	1.95 (1.57–2.42)	1.4×10^{-8}
rs183211, 17q21, 42143493, G/A	Stage 1	1812	575	0.22	0.28	1.45 (1.23–1.71)	1.37 (1.11–1.69)	2.29 (1.53–3.41)	2.5×10^{-5}
	Stage 2	8054	1264	0.23	0.25	1.20 (1.07–1.33)	1.13 (0.99–1.28)	1.62 (1.22–2.14)	1.1×10^{-3}
	Stages1+2	9866	1839	0.23	0.26	1.25 (1.15–1.37)	1.16 (1.04–1.29)	1.83 (1.46–2.28)	5.7×10^{-7}
	Stage 3	2204	442	0.22	0.26	1.25 (1.06–1.48)	1.15 (0.92–1.44)	1.79 (1.21–2.67)	0.018
	Combined	12070	2281	0.23	0.26	1.25 (1.16–1.35)	1.16 (1.05–1.27)	1.82 (1.5–2.21)	3.1×10^{-8}
rs4691139, 4q32.3, 166128171, A/G	Stage 1	1812	575	0.47	0.53	1.24 (1.08–1.42)	1.46 (1.13–1.88)	1.55 (1.16–2.05)	3.6×10^{-3}
	Stage 2	8054	1264	0.48	0.52	1.18 (1.08–1.29)	1.29 (1.10–1.50)	1.40 (1.17–1.67)	1.3×10^{-4}
	Stages1+2	9866	1839	0.48	0.52	1.20 (1.11–1.29)	1.33 (1.17–1.52)	1.44 (1.24–1.67)	1.1×10^{-6}
	Stage 3	2204	441	0.47	0.52	1.20 (1.04–1.39)	1.19 (0.91–1.54)	1.44 (1.08–1.94)	9×10^{-3}
	Combined	12070	2280	0.48	0.52	1.20 (1.17–1.38)	1.30 (1.16–1.46)	1.44 (1.26–1.65)	3.4×10^{-8}

*HRs estimated under the single disease risk models.

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the associations within a competing risks framework, revealed no association with breast cancer risk (Table 3). The ovarian cancer effect size was maintained in the competing risk analysis but the significance of the association was slightly weaker ($P=2\times10^{-6}$–1×10^{-5}). This is expected because 663 ovarian cancer cases occurring after a primary breast cancer diagnosis were excluded for this analysis. The evidence of association was somewhat stronger under the genotype-specific model (2-df $P=1.6\times10^{-9}$

Table 3. Analysis of associations with breast and ovarian cancer risk simultaneously (competing risks analysis) for SNPs found to be associated with breast or ovarian cancer.

SNP, Chr, Position, Allele1/Allele2	Unaffected (Allele2 Freq)	Ovarian Cancer (Allele2 Freq)	Breast Cancer (Allele2 Freq)	Ovarian Cancer		Breast Cancer	
				HR (95% CI)	P	HR (95% CI)	P
SNPs found to be associated with breast cancer risk.							
rs2290854, 1q32, 202782648, G/A	5473 (0.31)	1618 (0.31)	7259 (0.33)	1.08 (0.99–1.18)	0.08	1.14 (1.09–1.20)	2.7×10^{-8}
rs6682208, 1q32, 202832806, G/A	5471 (0.32)	1618 (0.33)	7260 (0.34)	1.08 (1.00–1.18)	0.06	1.13 (1.08–1.19)	1.2×10^{-7}
rs11196174, 10q25.3, 114724086, A/G	5471 (0.28)	1618 (0.29)	7257 (0.31)	1.07 (0.98–1.16)	0.16	1.14 (1.08–1.19)	3.2×10^{-7}
rs11196175, 10q25.3, 114726604, A/G	5465 (0.28)	1615 (0.29)	7247 (0.31)	1.07 (0.97–1.16)	0.16	1.14 (1.08–1.19)	3.9×10^{-7}
SNPs found to be associated with ovarian cancer risk							
rs17631303, 17q21, 40872185, A/G	5445 (0.19)	1610 (0.22)	7215 (0.19)	1.26 (1.14–1.39)	1.0×10^{-5}	1.02 (0.96–1.08)	0.52
rs183211, 17q21, 42143493, G/A	5473 (0.23)	1618 (0.26)	7260 (0.23)	1.25 (1.14–1.38)	3.5×10^{-6}	1.02 (0.97–1.08)	0.42
rs4691139, 4q32.3, 166128171, A/G	5473 (0.48)	1617 (0.53)	7269 (0.48)	1.21 (1.12–1.31)	2.8×10^{-6}	0.98 (0.93–1.02)	0.28

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and $P = 2.6\times10^{-9}$ for rs17631303 and rs183211 respectively in all samples combined) with larger HR estimates for the rare homozygote genotypes than those expected under a multiplicative model (Table 2).

Previous studies of the known common ovarian cancer susceptibility alleles found significant associations with ovarian cancer for both *BRCA1* and *BRCA2* carriers [6,7]. Thus, we evaluated the associations between the 17q21.31 SNPs and ovarian cancer risk for *BRCA2* carriers using iCOGS genotype data (7580 unaffected and 631 affected). Both rs17631303 and rs183211 were associated with ovarian cancer risk for *BRCA2* carriers ($P = 1.98\times10^{-4}$ and 9.26×10^{-4}), with similar magnitude and direction of association as for *BRCA1* carriers. Combined analysis of *BRCA1* and *BRCA2* mutation carriers provided strong evidence of association ($P = 2.80\times10^{-10}$ and 2.01×10^{-9}, Table 4).

The combined analysis of stage 1 and 2 samples, and *BRCA2* carriers, identified seven SNPs on the iCOGS array (pairwise r^2 range: 0.68–1.00) from a 1.3 Mb (40.8–42.1 Mb, build 36.3) region of 17q21.31 that were strongly associated ($P<1.27\times10^{-9}$) with ovarian cancer risk (Table 4, Figure 2). Stepwise-regression analysis based on observed genotype data retained only one of the seven SNPs in the model, but it was not possible to distinguish between the SNPs. Imputation through the 1000 Genomes Project, revealed several SNPs in 17q21.31 with stronger associations (Figure 2, Table S8) than the most significant genotyped SNP in the combined *BRCA1/2* analysis (rs169201, $P = 6.24\times10^{-11}$). The most significant SNP (rs140338099 (17-44034340), $P = 3\times10^{-12}$), located in *MAPT*, was highly correlated ($r^2 = 0.78$) with rs169201 in *NSF* (Figure 2). This locus appears to be distinct from a previously identified ovarian cancer susceptibility locus located >1 Mb distal on 17q21 (spanning 43.3–44.3 Mb, build 36.3) [30]. None of the SNPs in the novel region were strongly correlated with any of the SNPs in the 43.3–44.3 Mb region (maximum $r^2 = 0.07$, Figure S8). The most significantly associated SNP from the *BRCA1* GWAS from the 43.3–44.3 Mb locus was rs11651753 ($p = 4.6\times10^{-4}$) (Table 1) ($r^2<0.023$ with the seven most significant SNPs in the novel 17q21.31 region). An analysis of the joint associations of rs11651753 and rs17631303 from the two 17q21 loci with ovarian cancer risk for *BRCA1* carriers (Stage 1 and 2 samples) revealed that both SNPs remained significant in the model (P-for inclusion = 0.001 for rs11651753, 1.2×10^{-6} for rs17631303), further suggesting that the two regions are independently associated with ovarian cancer for *BRCA1* carriers.

The minor allele of rs4691139 at the novel 4q32.3 region was also associated with an increased ovarian cancer risk for *BRCA1* carriers (per-allele HR = 1.20, 95%CI:1.17–1.38, Table 2), but was not associated with breast cancer risk (Table 3). No other SNPs from the 4q32.3 region on the iCOGS array were more significantly associated with ovarian cancer for *BRCA1* carriers. Analysis of associations with variants identified through 1000 Genomes Project-based imputation of the Stage 1 and 2 samples, revealed 19 SNPs with stronger evidence of association ($P = 5.4\times10^{-7}$ to 1.1×10^{-6}) than rs4691139 (Figure S9). All were highly correlated (pairwise $r^2>0.89$) and the most significant (rs4588418) had $r^2 = 0.97$ with rs4691139. There was no evidence for association between rs4691139 and ovarian cancer risk for *BRCA2* carriers (HR = 1.08, 95%CI: 0.96–1.21, P = 0.22).

Absolute risks of developing breast and ovarian cancer

The current analyses suggest that 10 loci are now known to be associated with breast cancer risk for *BRCA1* mutation carriers: 1q32, 10q25.3, 19p13, 6q25.1, 12p11, *TOX3*, 2q35, *LSP1* and *RAD51L1* all reported here and *TERT* [31]. Similarly, seven loci are associated with ovarian cancer risk for *BRCA1* mutation

Table 4. Associations with SNPs at the novel 17q21 region with ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers.

SNP, Allele1/Allele2	*BRCA1* (Stage 1 & 2 samples)				*BRCA2*				*BRCA1* & *BRCA2* samples combined
	Unaffected (All2 freq)	Ovarian Cancer (All2 freq)	HR* (95%CI)	P-trend	Unaffected (All2 freq)	Ovarian Cancer (All2 freq)	HR* (95%CI)	P-trend	P-trend
rs17631303, A/G	9793 (0.19)	1831 (0.22)	1.27 (1.16–1.40)	3.04×10^{-7}	7481 (0.19)	626 (0.24)	1.32 (1.15–1.52)	1.98×10^{-4}	2.80×10^{-10}
rs2077606, G/A	9736 (0.19)	1810 (0.22)	1.27 (1.15–1.40)	5.51×10^{-7}	7421 (0.19)	613 (0.23)	1.31 (1.13–1.50)	5.60×10^{-4}	1.27×10^{-9}
rs2532348, A/G	9511 (0.21)	1789 (0.24)	1.25 (1.14–1.37)	8.71×10^{-7}	7407 (0.23)	615 (0.28)	1.33 (1.17–1.51)	4.62×10^{-5}	2.49×10^{-10}
rs183211, G/A	9866 (0.23)	1839 (0.26)	1.25 (1.15–1.37)	5.67×10^{-7}	7580 (0.25)	631 (0.30)	1.26 (1.11–1.43)	9.26×10^{-4}	2.01×10^{-9}
rs169201, A/G	9865 (0.20)	1839 (0.23)	1.27 (1.15–1.37)	5.04×10^{-7}	7578 (0.21)	631 (0.26)	1.36 (1.19–1.55)	1.72×10^{-5}	6.24×10^{-11}
rs199443, G/A	9849 (0.20)	1835 (0.23)	1.26 (1.15–1.39)	5.15×10^{-7}	7580 (0.21)	631 (0.26)	1.35 (1.18–1.54)	2.57×10^{-5}	8.87×10^{-11}
rs199534, A/C	9865 (0.20)	1839 (0.23)	1.26 (1.15–1.39)	6.26×10^{-7}	7575 (0.21)	630 (0.26)	1.35 (1.18–1.55)	1.90×10^{-5}	8.57×10^{-11}

*HRs estimated under the single disease risk model.

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carriers: 9p22, 8q24, 3q25, 17q21, 19p13, 17q21.31 and 4q32.3. Figure S10 shows the range of combined HRs at different percentiles of the combined genotype distribution, based on the single SNP HR and minor allele estimates from Table 1, Table 2, and Table S4 and for TERT from Bojesen et al [31] and assuming that all SNPs interact multiplicatively. Relative to *BRCA1* mutation carriers at lowest risk, the median, 5th and 95th percentile breast cancer HRs were 3.40, 2.27, and 5.35 respectively. These translate to absolute risks of developing breast cancer by age 80 of 65%, 51% and 81% for those at median, 5th and 95th percentiles of the combined genotype distribution (Figure 3, Figure S10). Similarly, the median, 5th and 95th percentile combined HRs for ovarian cancer were 6.53, 3.75 and 11.12 respectively, relative to those at lowest ovarian cancer risk (Figure S10). These HRs translate to absolute risks of developing ovarian cancer of 44%, 28% and 63% by age 80 for the median, 5th and 95th percentile of the combined genotype distribution (Figure 3).

Discussion

In this study we analyzed data from 11,705 *BRCA1* mutation carriers from CIMBA who were genotyped using the iCOGS high-density custom array, which included 31,812 SNPs selected on the basis of a *BRCA1* GWAS. This study forms the large-scale replication stage of the first GWAS of breast and ovarian cancer risk modifiers for *BRCA1* mutation carriers. We have identified a novel locus at 1q32, containing the *MDM4* oncogene, that is associated with breast cancer risk for *BRCA1* mutation carriers ($P<5\times10^{-8}$). A separate locus at 10q23.5, containing the *TCF7L2* gene, provided strong evidence of association with breast cancer risk for *BRCA1* carriers but did not reach a GWAS level of significance. We have also identified two novel loci associated with ovarian cancer for *BRCA1* mutation carriers at 17q21.31 and 4q32.2 ($P<5\times10^{-8}$). We further confirmed associations with loci previously shown to be associated with breast or ovarian cancer risk for *BRCA1* mutation carriers. In most cases stronger associations were detected with either the same SNP reported previously (due to increased sample size) or other SNPs in the regions. Future fine mapping studies of these loci will aim to identify potentially causal variants for the observed associations.

Although the 10q25.3 locus did not reach the strict GWAS level of significance for association with breast cancer risk, the association was observed at all three independent stages of the experiment. Additional evidence for the involvement of this locus in breast cancer susceptibility comes from parallel studies of the Breast Cancer Association Consortium (BCAC). SNPs at 10q25.3 had also been independently selected for inclusion on the iCOGS array through population based GWAS of breast cancer. Analyses of those SNPs in BCAC iCOGS studies also found that SNPs at 10q25.3 were associated with breast cancer risk in the general population [32]. Thus, 10q25.3 is likely a breast cancer risk-modifying locus for *BRCA1* mutation carriers. The most significant SNPs at 10q25.3 were located in *TCF7L2*, a transcription factor that plays a key role in the Wnt signaling pathway and in glucose homeostasis, and is expressed in normal and malignant breast tissue (The Cancer Genome Atlas (TCGA)). Variation in the *TCF7L2* locus has previously been associated with Type 2 diabetes in a number of GWAS. The most significantly associated SNPs with Type 2 diabetes (rs7903146 and rs4506565) [22,33] were also associated with breast cancer risk for *BRCA1* mutation carriers in stage 1 and 2 analyses ($p=3.7\times10^{-4}$ and $p=2.5\times10^{-4}$ respectively); these SNPs were correlated with the most significant hit (rs11196174) for *BRCA1* breast cancer ($r^2=0.40$ and 0.37 based

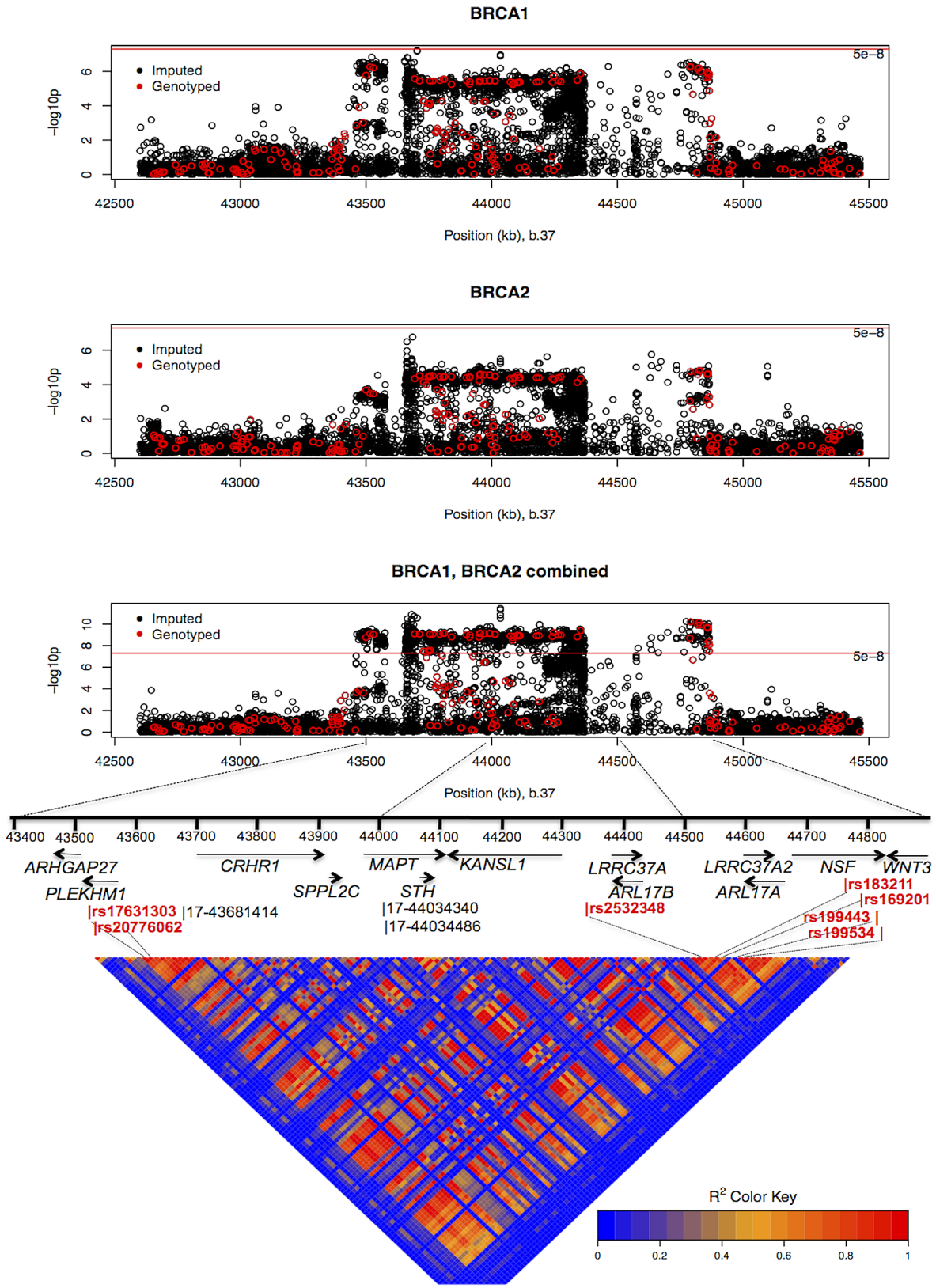

Figure 2. Mapping of the 17q21 locus. *Top 3 panels:* P-values of association ($-\log_{10}$ scale) with ovarian cancer risk for genotyped and imputed SNPs (1000 Genomes Project CEU), by chromosome position (b.37) at the 17q21 region, for *BRCA1*, *BRCA2* mutation carriers and combined. Results based on the kinship-adjusted score test statistic (1 d.f.). *Fourth panel:* Genes in the region spanning (43.4–44.9 Mb, b.37) and the location of the most significant genotyped SNPs (in red font) and imputed SNPs (in black font). *Bottom panel:* Pairwise r^2 values for genotyped SNPs on iCOG array in the 17q21 region covering positions (43.4–44.9 Mb, b.37).
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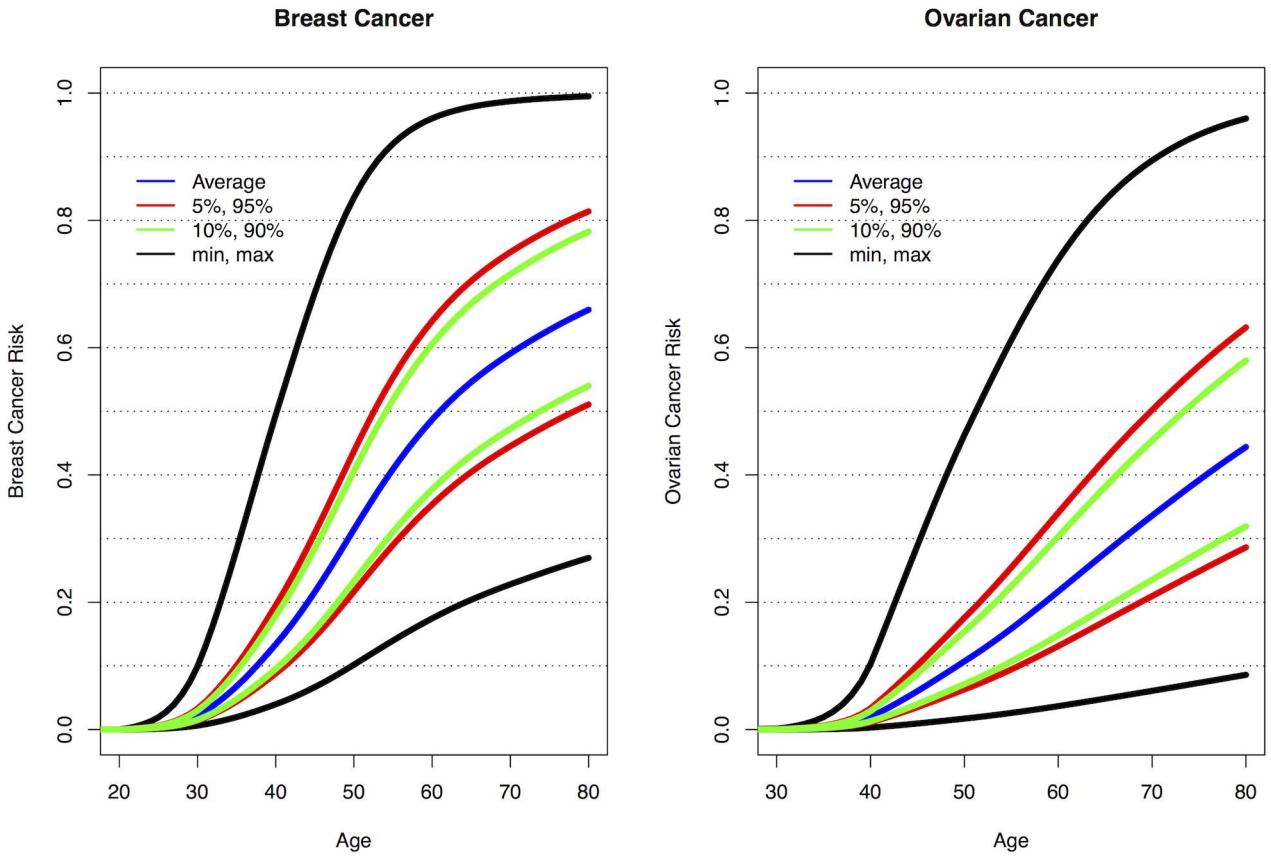

Figure 3. Predicted breast and ovarian cancer absolute risks for *BRCA1* mutation carriers at the 5th, 10th, 90th, and 95th percentiles of the combined SNP profile distributions. The minimum, maximum and average risks are also shown. Predicted cancer risks are based on the associations of known breast or ovarian cancer susceptibility loci (identified through GWAS) with cancer risk for *BRCA1* mutation carriers and loci identified through the present study. Breast cancer risks based on the associations with: 1q32, 10q25.3, 19p13, 6q25.1, 12p11, *TOX3*, 2q35, *LSP1*, *RAD51L1* (based on HR and minor allele frequency estimates from Table 1, Table 2, and Table S4) and *TERT* [31]. Ovarian cancer risks based on the associations with: 9p22, 8q24, 3q25, 17q21, 19p13 (Table 1) and 17q21.31, 4q32.3 (Table 2). Only the top SNP from each region was chosen. Average breast and ovarian cancer risks were obtained from published data [25]. The methods for calculating the predicted risks have been described previously [28].
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on stage 1 and 2 samples). This raises the possibility that variants in this locus influence breast cancer indirectly through effects on cellular metabolism.

We found that SNPs at 1q32 were primarily associated with ER-negative breast cancer risk for *BRCA1* mutation carriers. There was also evidence of association with ER-negative breast cancer for *BRCA2* mutation carriers. SNPs at the 1q32 region were independently selected for inclusion on iCOGS through GWAS of breast cancer in the general population by BCAC. In parallel analyses of iCOGS data by BCAC, 1q32 was found to be associated with ER-negative breast cancer [34] but not overall breast cancer risk [32]. Taken together, these results are in agreement with our findings and in line with the observation that the majority of *BRCA1* breast cancers are ER-negative. However, they are not in agreement with a previous smaller candidate-gene study that found an association between a correlated SNP in *MDM4* ($r^2>0.85$) and overall breast cancer risk [35]. The 1q32 locus includes the *MDM4* oncogene which plays a role in regulation of p53 and MDM2 and the apoptotic response to cell stress. *MDM4* is expressed in breast tissue and is amplified and overexpressed along with *LRRN2* and *PIK3C2B* in breast and other tumor types (TCGA) [36–38]. Although fine mapping will be necessary to identify the functionally relevant SNPs in this locus, we found evidence of cis-regulatory variation impacting *MDM4* expression [39–41] (Text S1, Table S9, Figure S11), suggesting that common variation in the 1q32 locus may influence the risk of breast cancer through direct effects on *MDM4* expression.

Several correlated SNPs at 17q21.31 from the iCOGS array provided strong evidence of association with ovarian cancer risk in both *BRCA1* and *BRCA2* mutation carriers. A subsequent analysis of these SNPs, which were selected through the *BRCA1* GWAS, in case-control samples from the Ovarian Cancer Association Consortium (OCAC), revealed that the 17q21.31 locus is associated with ovarian cancer risk in the general population [Wey et al, personal communication]. Thus, 17q21.31 is likely a novel susceptibility locus for ovarian cancer in *BRCA1* mutation carriers. The most significant associations at 17q21.31 were clustered in a large region of strong linkage disequilibrium which has previously been identified as a "17q21.31 inversion" (~900 kb long) consisting of two haplotypes (termed H1 and H2) [42]. The minor allele of rs2532348 (MAF = 0.21), which tags H2, was associated with increased ovarian cancer risk for *BRCA1* mutation carriers (Table 4). The 1.3 Mb 17q21.31 locus contains 13 genes and several predicted pseudogenes (Figure 2), several of which are

expressed in normal ovarian surface epithelium and ovarian adenocarcinoma [43]. Variation in this region has been associated with Parkinson's disease (*MAPT*, *PLEKHM1*, *NSF*, *c17orf69*) progressive supranuclear palsy (*MAPT*), celiac disease (*WNT3*), bone mineral density (*CRHR1*) (NHGRI GWAS catalog) and intracranial volume [44]. Of the top hits for these phenotypes, SNP rs199533 in *NSF*, previously associated with Parkinson's disease [45] and rs9915547 associated with intracranial volume [44] were strongly associated with ovarian cancer ($P<10^{-9}$ in *BRCA1/2* combined). Whether these phenotypes have shared causal variants in this locus remains to be elucidated. Further exploration of the functional relevance of the strongest hits in the 17q21.31 locus ($P<10^{-8}$ in *BRCA1/2* combined) provided evidence that cis-regulatory variation alters expression of several genes at 17q21, including *PLEKHM1*, *c17orf69*, *ARHGAP27*, *MAPT*, *KANSL1* and *WNT3* [39,41] (Table S9, Figure S12), suggesting that ovarian cancer risk may be associated with altered expression of one or more genes in this region.

Our analyses revealed that a second novel locus at 4q32.3 was also associated with ovarian cancer risk for *BRCA1* mutation carries ($P<5\times10^{-8}$). However, we found no evidence of association for these SNPs with ovarian cancer risk for *BRCA2* mutation carriers using 8,211 CIMBA samples genotyped using the iCOGS array. Likewise, no evidence of association was found between rs4691139 at 4q32.3 and ovarian cancer risk in the general population based on data by OCAC data derived from 18,174 cases and 26,134 controls (odds ratio = 1.00, 95%CI:0.97–1.04, P = 0.76) [46]. The confidence intervals rule out a comparable effect to that found in *BRCA1* carriers. Therefore, our findings may represent a *BRCA1*-specific association with ovarian cancer risk, the first of its kind. The 4q32.2 region contains several members of the *TRIM* (Tripartite motif containing) gene family, *c4orf39* and *TMEM192*. *TRIM60*, *c4orf39* and *TMEM192* are expressed in normal ovarian epithelium and/or ovarian tumors (TCGA).

In summary, we have identified a novel locus at 1q32 associated with breast cancer risk for *BRCA1* mutation carriers, which was also associated with ER-negative breast cancer for *BRCA2* carriers and in the general population. A separate locus at 10q23.5 provided strong evidence of association with breast cancer risk for *BRCA1* carriers. We have also identified 2 novel loci associated with ovarian cancer for *BRCA1* mutation carriers. Of these, the 4q32.2 locus was associated with ovarian cancer risk for *BRCA1* carriers but not for *BRCA2* carriers or in the general population. Additional functional characterisation of the loci will further improve our understanding of the biology of breast and ovarian cancer development in *BRCA1* carriers. Taken together with other identified genetic modifiers, 10 loci are now known to be associated with breast cancer risk for *BRCA1* mutation carriers (1q32, 10q25.3, 19p13, 6q25.1, 12p11, *TOX3*, 2q35, *LSP1*, *RAD51L1* and *TERT* and seven loci are known to be associated with ovarian cancer risk for *BRCA1* mutation carriers (9p22, 8q24, 3q25, 17q21, 19p13 and 17q21.31, 4q32.3).

As *BRCA1* mutations confer high breast and ovarian cancer risks, the results from the present study, taken together with other identified genetic modifiers, demonstrate for the first time that they can result in large differences in the absolute risk of developing breast or ovarian cancer for *BRCA1* between genotypes. For example, the breast cancer lifetime risks for the 5% of *BRCA1* carriers at lowest risk are predicted to be 28–50% compared to 81–100% for the 5% at highest risk (Figure 3). Based on the distribution of ovarian cancer risk modifiers, the 5% of *BRCA1* mutation carriers at lowest risk will have a lifetime risk of developing ovarian cancer of 28% or lower whereas the 5% at highest risk will have a lifetime risk of 63% or higher. Similarly, the breast cancer risk by age 40 is predicted to be 4–9% for the 5% of *BRCA1* carriers at lowest risk compared to 20–49% for the 5% at highest risk, whereas the ovarian cancer risk at age 50 ranges from 3–7% for the 5% at lowest risk and from 18–47% for the 5% at highest risk. The risks at all ages for the 10% at highest or lowest risk of breast and ovarian cancer are predicted to be similar to those for the highest and lowest 5%. Thus, at least 20% of BRCA1 mutation carriers are predicted to have absolute risks of disease that are different from the average *BRCA1* carriers. These large differences in cancer risks may have practical implications for the clinical management of *BRCA1* mutation carriers, for example in deciding the timing of interventions. Such risks, in combination with other lifestyle and hormonal risk factors could be incorporated into cancer risk prediction algorithms for use by clinical genetics centers. These algorithms could then be used to inform the development of effective and consistent clinical recommendations for the clinical management of *BRCA1* mutation carriers.

Supporting Information

Figure S1 Multidimensional scaling of stage 1 and stage 2 (genotyped on iCOGS) samples. Panel A: Graphical representation of the first two components, for the *BRCA1* carriers, for subgroups defined by the common 185delAG (c.68_69delAG) *BRCA1* Jewish founder mutation, the 5382insC (c.5266dupC) Eastern European founder mutation and Hapap individuals (CEU: European; ASI: Includes CHB and JPT populations; YRI: African). Panel B: Red dots represent the samples with >22% non-European ancestry, excluded from the analysis.
(PDF)

Figure S2 Genotyping cluster plots in the *BRCA1* samples for the key associated SNPs.
(PDF)

Figure S3 Quantile-quantile plot for the kinship adjusted score test statistic for stage 2 samples (1 degree of freedom χ^2 trend test) for the associations with breast cancer (panel A) and ovarian cancer (panel B) risk for *BRCA1* mutation carriers. The y = x line corresponds to the expected distribution, under the hypothesis of no inflation. Inflation was estimated using the values of the lowest 90% test statistics.
(PDF)

Figure S4 P-values (on $-\log_{10}$ scale) by chromosomal position, for the associations of 31,812 *BRCA1* GWAS SNPs with breast (panel A) and ovarian (panel B) cancer risk for *BRCA1* mutation carriers in the combined stage 1 and stage 2 samples. Blue lines correspond to a P-value of 10^{-5}; red lines correspond to P-value 5×10^{-8}.
(PDF)

Figure S5 Forest plots of the associations by country of residence of *BRCA1* mutation carriers in the combined stage 1, stage 2 and stage 3 samples for SNPs found to be associated with breast and ovarian cancer risk for *BRCA1* mutation carriers. Squares indicate the country specific, per-allele HR estimates for the SNPs. The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% confidence intervals. There was some evidence of heterogeneity in country-specific HR estimates for the rs2290854 and rs6682208 SNP (P = 0.04 and 0.02 respectively, Figure S3), but after accounting for opposite effects of these SNPs in Finland/Denmark, there was no evidence of heterogeneity. There was some evidence of heterogeneity in the country-specific HRs for rs17631303 (P-het = 0.004, df = 19) but this was no longer present after excluding one country (Poland, P-

het = 0.12, df = 18), or when restricting analyses to Stage 1 and 2 samples only (P-het = 0.09, df = 19). There was no evidence of heterogeneity for correlated SNP rs183211 (P-het = 0.10). There was no evidence of hereterogeneity in the country-specific HRs for any of the other SNPs (P>0.68).
(PDF)

Figure S6 *MDM4* regional association plot using *BRCA1* stage 1 and stage 2 samples. P-values for association ($-\log_{10}$ scale) with breast cancer risk for *BRCA1* mutation carriers for genotyped SNPs (diamond symbols ◇) and SNPs imputed from the 1000 genomes project data (square symbols □), by position (hg18) on chromosome 1. Red gradient represents r^2 value with the most significant genotyped SNP rs4951407. The blue peaks represent recombination rate in the region.
(PDF)

Figure S7 *TCF7L2* regional association plot using *BRCA1* stage 1 and stage 2 samples. P-values for association ($-\log_{10}$ scale) with breast cancer risk for *BRCA1* mutation carriers for genotyped SNPs (diamond symbols ◇) and SNPs imputed from the 1000 genomes project data (square symbols □), by position (hg18) on chromosome 1. Missing genotypes were replaced by imputed results. Red gradient represents r^2 value with the most significant genotyped SNP rs11196174. The blue peaks represent recombination rate in the region.
(PDF)

Figure S8 Linkage disequilibrium patterns between the SNPs in the novel (17q21.31) and previously identified regions on 17q21. SNPs in the novel region are uncorrelated with SNPs in the 43.3–44.3 Mb region (positions according to hg build 36.3).
(PDF)

Figure S9 4q32.3 regional association plot using *BRCA1* stage 1 and stage 2 samples. P-values for association ($-\log_{10}$ scale) with ovarian cancer risk for *BRCA1* mutation carriers for genotyped SNPs (diamond symbols ◇) and imputed SNPs from the 1000 genomes project data (square symbols □), by position (hg18) on chromosome 1. Red gradient represents r^2 value with the most significant genotyped SNP rs4691139. Blue peaks represent recombination rate in the region.
(PDF)

Figure S10 Combined Hazard Ratios (HR) for breast and ovarian cancer for *BRCA1* mutation carriers. (A) HR for Breast Cancer based on 10 loci associated with breast cancer risk for *BRCA1* mutation carriers. (B) Ovarian Cancer based on 7 loci associated with ovarian cancer risk for *BRCA1* mutation carriers. All HRs computed relative to the lowest risk category. The Y-axes translate the combined HRs into absolute risks of developing breast or ovarian cancer by age 80. The absolute risks and HRs at different percentiles of the combined genotype distribution are also marked. The combined HRs were obtained under the assumption that the loci interact multiplicatively.
(PDF)

Figure S11 Cis-eQTL and allelic expression (AE) analyses at *MDM4* locus. A) Cis-eQTLs for SNPs at *MDM4* locus using expression data from primary human osteoblasts (HOb). B) AE mapping for cis-regulatory variation in *MDM4* locus using primary skin fibroblasts. Coordinates (hg18) for locus shown on top; blue tracks indicate the $-\log_{10}$(P value) of the association across all SNPs tested. The location of transcripts in this region is shown below.
(PDF)

Figure S12 Cis-eQTL and allelic expression (AE) analyses at chr17q21.31 locus. (Upper panel) Cis-eQTLs for SNPs at c17orf69 locus using expression data from primary human osteoblasts. Allelic expression mapping for cis-regulatory variation in *KANSL1* (middle panel) and *WNT3* loci (lower panel) using a CEU population panel of lymphoblastoid cells. Coordinates (hg18) for loci are shown on top; blue tracks indicate the $-\log_{10}$(P value) of the association across all SNPs tested. The location of transcripts in these regions are shown.
(PDF)

Table S1 Affected and unaffected *BRCA1* mutation carriers by study country in the breast and ovarian cancer analysis used in SNP selection for the iCOGS array.
(DOCX)

Table S2 Origin of *BRCA1* samples by Country and Stage used in the current analysis.
(DOCX)

Table S3 Sample and SNP quality control summary.
(DOCX)

Table S4 Associations with breast cancer risk for *BRCA1* mutation carriers, for known breast cancer susceptibility variants.
(DOCX)

Table S5 Associations with *BRCA1* breast or ovarian cancer risk for SNPs genotyped at stages 1, 2, and 3.
(DOCX)

Table S6 Analysis of breast cancer associations by *BRCA1* mutation class.
(DOCX)

Table S7 Associations with Breast Cancer ER status in *BRCA1* carriers for SNPs genotyped in stages 1–3.
(DOCX)

Table S8 Imputed SNPs at the novel 17q21 region with P-values less than the most significant genotyped SNP (rs169201).
(DOCX)

Table S9 SNPs associated ($P<1\times10^{-5}$) with local expression and Allelic Imbalance.
(DOCX)

Text S1 Supplementary Methods.
(DOCX)

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Identification and molecular characterization of a new ovarian cancer susceptibility locus at 17q21.31

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Collated and organized samples for genotyping: SJR and CMP.
Genotyping: JMC, DCT, FB, and DV.
Data analysis: JPW, JT, H-YL, YAC, BLF, MLL, and Y-Y T.
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Abstract

Epithelial ovarian cancer (EOC) has a heritable component that remains to be fully characterized. Most identified common susceptibility variants lie in non-protein-coding sequences. We hypothesized that variants in the 3′ untranslated region at putative microRNA (miRNA) binding sites represent functional targets that influence EOC susceptibility. Here, we evaluate the association between 767 miRNA binding site single nucleotide polymorphisms (miRSNPs) and EOC risk in 18,174 EOC cases and 26,134 controls from 43 studies genotyped through the Collaborative Oncological Gene-environment Study. We identify several miRSNPs associated with invasive serous EOC risk (OR=1.12, $P=10^{-8}$) mapping to an inversion polymorphism at 17q21.31. Additional genotyping of non-miRSNPs at 17q21.31 reveals stronger signals outside the inversion ($P=10^{-10}$). Variation at 17q21.31 associates with neurological diseases, and our collaboration is the first to report an association with EOC susceptibility. An integrated molecular analysis in this region provides evidence for *ARHGAP27* and *PLEKHM1* as candidate EOC susceptibility genes.

Genome wide association studies (GWAS) have identified hundreds of genetic variants conferring low penetrance susceptibility to cancer[1]. More than 90% of these variants lie in non protein-encoding sequences including non-coding RNAs and regions containing regulatory elements (i.e. enhancers, promoters, untranslated regions (UTRs))[1]. The emerging hypothesis is that common variants within non-coding regulatory regions influence expression of target genes, thereby conferring disease susceptibility[1].

MicroRNAs (miRNAs) are short non-coding RNAs that regulate gene expression post-transcriptionally by binding primarily to the 3′ UTR of target messenger RNA (mRNA), causing translational inhibition and/or mRNA degradation[2-4]. MiRNAs have been shown to play a key role in the development of epithelial ovarian cancer (EOC) [2]. We [5,6] and others [7] have found evidence that various miRNA-related single nucleotide polymorphisms (miRSNPs) are associated with EOC risk, suggesting they may be key disruptors of gene function and contributors to disease susceptibility [8,9]. However, studies of miRSNPs that affect miRNA-mRNA binding have been restricted by small sample sizes and therefore have limited statistical power to identify associations at genome wide levels of significance[7-9]. Larger-scale studies and more systematic approaches are warranted to fully evaluate the role of miRSNPs and their contribution to disease susceptibility.

Here, we use the *in silico* algorithms, TargetScan [10,11] and Pictar [12,13] to predict miRNA:mRNA binding regions involving genes and miRNAs relevant to EOC, and align identified regions with SNPs in the dbSNP database (Methods). We then genotype 1,003 miRSNPs (or tagging SNPs with $r^2>0.80$) in 18,174 EOC cases and 26,134 controls from 43 studies from the Ovarian Cancer Association Consortium (OCAC) (Supplementary Table S1). Genotyping was performed on a custom Illumina Infinium iSelect array designed as part of the Collaborative Oncological Gene-environment Study (COGS), an international effort that evaluated 211,155 SNPs and their association with ovarian, breast, and prostate cancer risk. Our investigation uncovers 17q21.31 as a new susceptibility locus for EOC, and we provide insights into candidate genes and possible functional mechanisms underlying disease development at this locus.

Results

Association analyses

Seven hundred and sixty-seven of the 1,003 miRSNPs passed genotype quality control (QC) and were evaluated for association with invasive EOC risk; most of the miRSNPs that failed QC were monomorphic (see Methods). Primary analysis of 14,533 invasive EOC cases and 23,491 controls of European ancestry revealed four strongly correlated SNPs (r^2=0.99; rs1052587, rs17574361, rs4640231, and rs916793) that mapped to 17q21.31 and were associated with increased risk (per allele odds ratio (OR) = 1.10, 95% CI 1.06-1.13) at a genome-wide level of significance (10^{-7}); no other miRSNPs had associations stronger than $P<10^{-4}$ (Supplementary Fig. S1). The most significant association was for rs1052587 (P=1.9×10^{-7}), and effects varied by histological subtype, with the strongest effect observed for invasive serous EOC cases (OR=1.12, P=4.6×10^{-8}) (Table 1). No heterogeneity in ORs was observed across study sites (Supplementary Fig. S2).

Rs1052587, rs17574361, and rs4640231 reside in the 3′UTR of microtubule-associated protein tau (*MAPT*), KAT8 regulatory NSL complex subunit 1 (*KANSL1/KIAA1267*), and corticotrophin releasing hormone receptor 1 (*CRHR1*) genes, at putative binding sites for miR-34a, miR-130a, and miR-34c, respectively. The fourth SNP, rs916793, is perfectly correlated with rs4640231 and lies in a non-coding RNA, *MAPT*-antisense 1. 17q21.31 contains a ~900kb inversion polymorphism[14] (ch 17: 43,624,578-44,525,051 MB, human genome build 37), and all three miRSNPs and the tagSNP are located within the inversion (Fig. 1).

Chromosomes with the non-inverted or inverted segments of 17q21.31, respectively known as haplotype 1 (H1) and haplotype 2 (H2), represent two distinct lineages that diverged ~3 million years ago and have not undergone any recombination event [14]. The four susceptibility alleles identified here reside on the H2 haplotype that is reported to be rare in Africans and East Asians, but is common (frequency >20%) and exhibits strong linkage disequilibrium (LD) among Europeans [14], consistent with our findings. The H2 haplotype has a frequency of 22% among European women in our primary analysis (Table 1) but only 3.2% and 0.3% among Africans (151 invasive cases, 200 controls) and Asians (716 invasive cases, 1573 controls), respectively.

To increase genomic coverage at this locus, we evaluated an additional 142 non-miRSNPs at 17q21.31 that were also genotyped as part of COGS in the same series of OCAC cases and controls. We also imputed genotypes using data from the 1000 Genomes Project[15]. These approaches identified a second cluster of strongly correlated SNPs (r^2>0.90) in a distinct region proximal to the inversion (centered at chromosome 17: 43.5 MB, human genome build 37) that was more significantly associated with the risk of all invasive EOCs (P= 10^{-9}) and invasive serous EOC specifically (P= 10^{-10}) than the cluster of identified miRSNPs (Fig. 1). Association results and annotation for SNPs in this second cluster are shown in Supplementary Table S2; this cluster includes three directly genotyped SNPs (rs2077606, rs17631303, and rs12942666), with the strongest association observed for rs2077606 among all invasive cases (OR=1.12, 95% CI: 1.08-1.16), P=7.8×10^{-9}) and invasive serous cases (OR=1.15, 95% CI: 1.12-1.19, P=3.9×10^{-10}). These SNPs were chosen for genotyping in COGS because they had shown evidence of association as modifiers of EOC risk in BRCA1 gene mutation carriers by the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)[16]. Several imputed SNPs in strong LD (r^2>0.90) were more strongly associated with risk than their highly correlated genotyped SNPs (Supplementary Table S2). This risk-associated region at 17q21.31 is distinct from a previously reported ovarian cancer susceptibility locus at 17q21[17]; neither the genotyped or imputed SNPs we report here are

strongly correlated (maximum r^2= 0.01) with SNPs from the 17q21 locus (spanning 46.2-46.5 MB, build 37).

Genotype clustering was poor for rs2077606, but clustering was good for its correlated SNP, rs12942666 (r^2=0.99), and so results for this SNP are presented instead (Supplementary Fig. S2; Table 1). Subgroup analysis revealed marginal evidence of association for rs12942666 with endometrioid (*P*=0.04), but not mucinous or clear cell EOC subtypes (Table 1), and results were consistent across studies (Supplementary Fig. S4). Rs12942666 is correlated with the top-ranked miRSNP, rs1052587 (r^2=0.76) (Fig. 1). To evaluate whether associations observed for rs12942666 and rs1052587 represented independent signals, stepwise logistic regression was used; only rs12942666 was retained in the model. This suggests that the cluster which includes rs12942666 is driving the association with EOC risk that was initially identified through the candidate miRSNPs.

Functional and molecular analyses

To evaluate functional evidence for candidate genes, risk-associated SNPs, and regulatory regions at 17q21.31, we examined a one megabase region centered on rs12942666 using a combination of locus specific and genome-wide assays and *in silico* analyses of publicly available datasets, including The Cancer Genome Atlas (TCGA) Project[18] (see Methods). Rs12942666 and many of its correlated SNPs lie within introns of Rho GTPase activating protein 27 (*ARHGAP27*) or its neighboring gene, pleckstrin homology domain containing, family M (with RUN domain) member 1 (*PLEKHM1*) (Supplementary Table S2). There are another 15 known protein-coding genes within the region: *KIF18B, C1QL1, DCAKD, NMT1, PLCD3, ABCB4, HEXIM1, HEXIM2, FMNL1, C17orf46, MAP3K14, C17orf69, CRHR1, IMP5*, and *MAPT* (Fig. 2a).

To evaluate the likelihood that one or more genes within this region represent target susceptibility gene(s), we first analyzed expression, copy number variation, and methylation involving these genes in EOC tissues and cell lines (Fig. 2b-g; Supplementary Tables S3 and S4). Most genes showed significantly higher expression ($P<10^{-4}$) in EOC cell lines versus normal ovarian cancer-precursor tissues (OCPTs); *ARHGAP27* showed the most pronounced difference in gene expression between cancer and normal cells ($P=10^{-16}$) (Fig. 2b and Supplementary Table S3). For nine genes, we also found overexpression in primary high-grade serous (HGS) EOC tumors versus normal ovarian tissue in at least one of two publicly available datasets, The Cancer Genome Atlas (TCGA) of 568 tumors [18]and/or the Gene Expression Omnibus (GEO) series GSE18520 dataset consisting of 53 tumors[19] (Fig. 2c and Supplementary Table S3). Analysis of DNA copy number variation in TCGA revealed frequent loss of heterozygosity in this region rather than gains (Supplementary Fig. 5a-b; Supplementary Methods). We observed significant hypomethylation (*P*<0.01) in ovarian tumors compared to normal tissue for *DCAKD, PLCD3, ACBD4, FMNL1*, and *PLEKHM1* (Fig. 2d and Supplementary Table S4), which is consistent with the overexpression observed for *DCAKD, PLCD3*, and *FMNL1*. Taken together, these data suggest that the mechanism underlying overexpression may be epigenetic rather than based on copy number alterations.

We evaluated associations between genotypes for the top risk SNP rs12942666 (or a tagSNP) and expression of all genes in the region (expression quantitative trait locus (eQTL) analysis) in normal OCPTs, lymphoblastoid cell lines (LCLs), and primary tumors from TCGA. We observed significant eQTL associations (P<0.05) in normal OCPTs only for *ARHGAP27* (*P*=0.04) (Fig. 2e; Supplementary Table S3). Because rs12942666 was not genotyped in tissues analyzed in TCGA, we used data for its correlated SNP rs2077606 (r^2=0.99) to evaluate eQTLs in tumor tissues. Rs2077606 genotypes were strongly associated with *PLEKHM1* expression in primary HGS-EOCs ($P=1\times10^{-4}$) (Fig. 2f;

Supplementary Table S3). We also detected associations between rs12942666 (and rs2077606) genotypes and methylation for *PLEKHM1* and *CRHR1* in primary tumors (P=0.020 and 0.001, respectively) using methylation quantitative trait locus (mQTL) analyses (Fig. 2g; Supplementary Table S4). Finally, the Catalogue of Somatic Mutations in Cancer (COSMIC) database [20] showed that nine genes in the region, including *PLEKHM1*, have functionally significant mutations in cancer, although for most genes mutations were not reported in ovarian carcinomas (Supplementary Table S3).

Taken together, these data suggest that several genes at the 17q21.31 locus may play a role in EOC development. The risk-associated SNPs we identified fall within non-coding DNA, suggesting the functional SNP(s) may be located within an enhancer, insulator, or other regulatory element that regulates expression of one of the candidate genes we evaluated. One hypothesis emerging from these molecular analyses is that rs12942666 (or a correlated SNP) mediates regulation of *PLEKHM1*, a gene implicated in osteopetrosis and endocytosis [21] and/or *ARHGAP27*, a gene that may promote carcinogenesis through dysregulation of Rho/Rac/Cdc42-like GTPases [22]. To identify the most likely candidate for being the causal variant at 17q21.31, we compared the difference between log-likelihoods generated from un-nested logistic regression models for rs12942666 and each of 198 SNPs in a 1 MB region featured in Supplementary Table 2. As expected, the log likelihoods were very similar due to the strong LD; no SNPs emerged as having a likelihood ratio greater than 20 for being the causal variant.

To explore the possible functional significance of rs12942666 and strongly correlated variants (r^2>0.80), we then generated a map of regulatory elements around rs12942666 using ENCODE data and FAIRE-seq analysis of OCPTs (Supplementary Methods). We observed no evidence of putative regulatory elements coinciding with rs12942666 or correlated SNPs (Fig. 3a). A map of regulatory elements in the entire 1 MB region can be seen in Supplementary Fig. 5c-f. We subsequently used *in silico* tools (ANNOVAR[23], SNPinfo[24], and SNPnexus[25]) to evaluate the putative function of possible causal SNPs (Supplementary Methods). Of 50 SNPs with possible functional roles, more than 30 reside in putative transcription factor binding sites (TFBS) within or near *PLEKHM1* or *ARHGAP27*; 12 SNPs may affect methylation or miRNA binding, and two are non-synonymous coding variants predicted to be of no functional significance (Supplementary Table S2).

Since most of the top-ranked 17q21.31 SNPs with putative functions (including two of the top directly genotyped SNPs, rs2077606 and rs17631303), are predicted to lie in TFBS (Supplementary Table S2), we used the *in silico* tool, JASPAR [26] to further examine TFBS coinciding with these SNPs. Two SNPs scored highly in this analysis (Supplementary Table S5); the first, rs12946900, lies in a GAGGAA motif and canonical binding site for *SPIB*, an Ets family member[27]. Ets factors have been implicated in the development of ovarian cancer and other malignancies[28], but little evidence supports a specific role for *SPIB* in EOC etiology. The second hit was for rs2077606, which lies in an E-box motif CACCTG at the canonical binding site for *ZEB1* (chr. 10p11.2), a zinc-finger E-box binding transcription factor that represses E-cadherin[29,30] and contributes to epithelial-mesenchymal transition in EOCs [31].

We analyzed expression of *SPIB* and *ZEB1* in primary ovarian cancers using TCGA data; we found no significant difference in *SPIB* expression in tumors compared to normal tissues (Fig. 3bi). In contrast, *ZEB1* expression was significantly lower in primary HGS-EOCs compared to normal tissues (P=0.005) (Fig. 3bii). We validated this finding using qPCR analysis in 123 EOC and OCPT cell lines (P=8.8 $\times 10^{-4}$) (Fig. 3biii). Since rs2077606 lies within an intron of *PLEKHM1*, this gene is a candidate target for *ZEB1* binding at this site.

Our eQTL analysis also suggests *ARHGAP27* is a strong candidate *ZEB1* target at this locus; *ARHGAP27* expression is highest in OCPT cell lines carrying the minor allele of rs2077606 (P=0.034) (Figure 3ci). Although we observed no eQTL associations between rs2077606 and *ZEB1* expression in LCLs (Figure 3cii), we found evidence of eQTL between rs2077606 and *ZEB1* expression in HGS-EOCs (P=0.045) (Figure 3ciii). *ZEB1* binding at the site of the common allele is predicted to repress gene expression while loss of *ZEB1* binding conferred by the minor allele may enable expression of *ARHGAP27*, consistent with the eQTL association in OCPTs (Fig. 3ci). Although this data supports a repressor role for *ZEB1* in EOC development and suggests ARHGAP27 may be a functional target of rs2077606 (or a correlated SNP) in OCPTs through trans-regulatory interactions with *ZEB1*, it is important to investigate additional hypotheses as we continue to narrow down the list of target susceptibility genes, SNPs, and regulatory mechanisms that contribute to EOC susceptibility at this locus.

Discussion

The present study represents the largest, most comprehensive investigation of the association between putative miRSNPs in the 3′ untranslated region and cancer risk. This and the systematic follow-up to evaluate associations with EOC risk for non-miRSNPs in the region identified 17q21.31 as a new susceptibility locus for EOC. Although the miRSNPs identified here may have some biological significance, our findings suggest that other types of variants in non-coding DNA, especially non-miRSNPs at the 17q21.31 locus, are stronger contributors to EOC risk. It is possible, however, that highly significant miRSNPs exist that were not identified in our study because a) they were not pre-selected for evaluation (i.e. they do not reside in a binding site involving miRNAs or genes with known relevance to EOC, or they reside in regions other than the 3′UTR[3,4]) and/or b) they were very rare and could not be designed or detected with our genotyping platform and sample size, respectively. Despite these limitations, the homogeneity between studies of varying designs and populations in the OCAC and the genome-wide levels of statistical significance imply that all detected associations are robust. Furthermore, molecular correlative analyses of genes within the region suggest that cis-acting genetic variants influencing non-coding DNA regulatory elements, miRNAs, and/or methylation underlie disease susceptibility at the 17q21.31 locus. Finally, these studies point to a subset of candidate genes (i.e. *PLEKHM1, ARHGAP27*) and transcription factors (i.e. ZEB1) that may influence EOC initiation and development.

This novel locus is one of eleven loci now identified that contains common genetic variants conferring low penetrance susceptibility to EOC in the general population [17,32,33,34]. Genetic variants at several of these loci influence risks of more than one cancer type, suggesting that several cancers may share common mechanisms. For example, alleles at 5p15.33 and 19p13.1 are associated with estrogen-receptor-negative breast cancer and serous EOC susceptibility [32,35], and variants at 8q24 are associated with risk of EOC and other cancers [17,36]. Genetic variation at 17q21.31 is also associated with frontotemporal dementia-spectrum disorders, Parkinson's disease, developmental delay, and alopecia [37-42]. Through COGS, the CIMBA also recently identified 17q21.31 variants as modifying EOC risk in *BRCA1* and *BRCA2* carriers ($P<10^{-8}$ in *BRCA1/2* combined)[16]. In particular, rs17631303, which is perfectly correlated with rs2077606 and rs12942666, was among the top-ranking SNPs detected by CIMBA[16]. Consistent with our findings, CIMBA also provide data that suggests EOC risk is associated with altered expression of one or more genes in the 17q21.31 region[16]. Thus, results from this large-scale collaboration support a role for this locus in both *BRCA1/2* and non-*BRCA1/2* mediated EOC development. Before these findings can be integrated with variants from other confirmed loci and non-genetic factors to predict women at greatest risk of developing EOC and provide options for medical

management of these risks, continued efforts will be needed to fine map the 17q21.31 region and to fully characterize the functional and mechanistic effects of potential causal SNPs in disease etiology and development.

Methods

Study population

Forty-three individual OCAC studies contributed samples and data to the COGS initiative. Nine of the 43 participating studies were case-only (GRR, HSK, LAX, ORE, PVD, RMH, SOC, SRO, UKR); cases from these studies were pooled with case-control studies from the same geographic region. The two national Australian case-control studies were combined into a single study to create 34 case-control sets. Details regarding the 43 participating OCAC studies are summarized in Supplementary Table S1. Briefly, cases were women diagnosed with histologically confirmed primary EOC (invasive or low malignant potential), fallopian tube cancer, or primary peritoneal cancer ascertained from population- and hospital-based studies and cancer registries. The majority of OCAC cases (>90%) do not have a family history of ovarian or breast cancer in a first-degree relative, and most have not been tested for *BRCA1/2* mutations as part of their parent study. Controls were women without a current or prior history of ovarian cancer with at least one ovary intact at the reference date. All studies had data on disease status, age at diagnosis/interview, self-reported racial group, and histologic subtype. Most studies frequency-matched cases and controls on age-group and race.

Selection of Candidate Genes and SNPs

To increase the likelihood of identifying miRSNPs with biological relevance to EOC, we reviewed published literature and consulted public databases to generate two lists of candidate genes: 1) 55 miRNAs reported to be deregulated in EOC tumors compared to normal tissue in at least one study [43-46], and 2) 665 genes implicated in the pathogenesis of EOC through gene expression analyses [47,48], somatic mutations [49], or genetic association studies [50,51]. Many genes were identified through the Gene Prospector database[51], a web-based application that selects and prioritizes potential disease-related genes using a highly curated, up-to-date database of genetic association studies.

Using each candidate gene list as input, we identified putative sites of miRNA:mRNA binding with the computational prediction algorithms TargetScan version 5.1 [10,11] and PicTar [12,13] and Supplementary Methods). Each algorithm generated start and end coordinates for regions of miRNA binding, and database SNP (dbSNP)[52] version 129 was mined to identify SNPs falling within the designated binding regions. Of 3,246 unique miRSNPs that were identified, 1102 obtained adequate design scores using Illumina's Assay Design Tool. The majority (n=1085, 98.5%) of the 1102 SNPs resided in predicted sites of miRNA binding (and therefore represent miRSNPs), while the remainder (n=17) are tagSNPs ($r^2 > 0.80$) for miRSNPs that were not designable or had poor to moderate design scores. Ninety nine of the 1102 SNPs failed during custom assay development, leaving a total of 1,003 SNPs that were designed and genotyped.

Genotyping and QC

The candidate miRSNPs selected for the current investigation were genotyped using a custom Illumina Infinium iSelect Array as part of the international Collaborative Oncological Gene-environment Study (COGS), an effort to evaluate 211,155 genetic variants for association with the risk of ovarian, breast, and prostate cancer. Samples and data were included from several consortia, including OCAC, the Breast Cancer Association Consortium (BCAC), the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA),

and the Prostate Cancer Association Group to Investigate Cancer- Associated Alterations in the Genome (PRACTICAL). Although one of the primary goals of COGS was to replicate and fine-map findings from pooled genome-wide association studies (GWAS) from each consortia, this effort also aimed to genotype candidate SNPs of interest (such as the miRSNPs). The genotyping and QC process has been described recently in our report of OCAC's pooled GWAS findings[34]. Briefly, COGS genotyping was conducted at six centers, two of which were used for OCAC samples: McGill University and Génome Québec Innovation Centre (Montréal, Canada) (n=19,806) and Mayo Clinic Medical Genomics Facility (n=27,824). Each 96-well plate contained 250ng genomic DNA (or 500 ng whole genome-amplified DNA). Raw intensity data files were sent to the COGS data coordination center at the University of Cambridge for genotype calling and QC using the GenCall algorithm.

Sample QC—One thousand two hundred and seventy three OCAC samples were genotyped in duplicate. Genotypes were discordant for greater than 40 percent of SNPs for 22 pairs. For the remaining 1,251 pairs, concordance was greater than 99.6 percent. In addition we identified 245 pairs of samples that were unexpected genotypic duplicates. Of these, 137 were phenotypic duplicates and judged to be from the same individual. We used identity-by-state to identify 618 pairs of first-degree relatives. Samples were excluded according to the following criteria: 1) 1,133 samples with a conversion rate (the proportion of SNPs successfully called per sample) of less than 95 percent; 2) 169 samples with heterozygosity >5 standard deviations from the intercontinental ancestry specific mean heterozygosity; 3) 65 samples with ambiguous sex; 4) 269 samples with the lowest call rate from a first-degree relative pair 5) 1,686 samples that were either duplicate samples that were non-concordant for genotype or genotypic duplicates that were not concordant for phenotype. A total of 44,308 eligible subjects including 18,174 cases and 26,134 controls were available for analysis.

SNP QC—The process of SNP selection by the participating consortia has been summarized previously[34]. In total, 211,155 SNP assays were successfully designed, including 23,239 SNPs nominated by OCAC. Overall, 94.5% of OCAC-nominated SNPs passed QC. SNPs were excluded if: (1) the call rate was less than 95% with MAF > 5% or less than 99% with MAF < 5% (n=5,201); (2) they were monomorphic upon clustering (n=2,587); (3) p values of HWE in controls were less than 10^{-7} (n=2,914); (4) there was greater than 2% discordance in duplicate pairs (n=22); (5) no genotypes were called (n=1,311). Of 1,003 candidate miRSNPs genotyped, 767 passed QC criteria and were available for analysis; the majority of miRSNPs that were excluded were monomorphic (n=158, 67%). Genotype intensity cluster plots were visually inspected for the most strongly associated SNPs.

Population stratification

HapMap DNA samples for European (CEU, n=60), African (YRI, n=53) and Asian (JPT +CHB, n=88) populations were also genotyped using the COGS iSelect. We used the program LAMP [53] to estimate intercontinental ancestry based on the HapMap (release no. 23) genotype frequency data for these three populations. Eligible subjects with greater than 90 percent European ancestry were defined as European (n=39,773) and those with greater than 80 percent Asian or African ancestry were defined as Asian (n=2,382) or African respectively (n=387). All other subjects were defined as being of mixed ancestry (n=1,766). We then used a set of 37,000 unlinked markers to perform principal components analysis within each major population subgroup. To enable this analysis on very large sample sizes we used an in-house program written in C++ using the Intel MKL libraries for eigenvectors (available at http://ccge.medschl.cam.ac.uk/software/).

Tests of association

We used unconditional logistic regression treating the number of minor alleles carried as an ordinal variable (log-additive model) to evaluate the association between each SNP and EOC risk. Separate analyses were carried out for each ancestry group. The model for European subjects was adjusted for population substructure by including the first 5 eigenvalues from the principal components analysis. African- and Asian- ancestry-specific estimates were obtained after adjustment for the first two components representing each respective ancestry. Due to the heterogeneous nature of EOC, subgroup analysis was conducted to estimate genotype-specific odds ratios for serous carcinomas (the most predominant histologic subtype) and the three other main histological subtypes of EOC: endometrioid, mucinous, and clear cell. Separate analyses were also carried out for each study site, and site-specific ORs were combined using a fixed-effect meta-analysis. The I^2 test of heterogeneity was estimated to quantify the proportion of total variation due to heterogeneity across studies, and the heterogeneity of odds ratios between studies was tested with Cochran's Q statistic. The R statistical package 'r-meta' was used to generate forest plots. Statistical analysis was conducted in PLINK[54].

Imputation of genotypes at 17q21.31

To increase genomic coverage, we imputed genotype data for the 17q21.31 region (chr17: 40,099,001-44,900,000, human genome build 37) with IMPUTE2.2 [55] using phase 1 haplotype data from the January 2012 release of the 1000 genome project data [15]. For each imputed genotype the expected number of minor alleles carried was estimated (as weights). IMPUTE provides estimated allele dosage for SNPs that were not genotyped and for samples with missing data for directly genotyped SNPs. Imputation accuracy was estimated using an r^2quality metric. We excluded imputed SNPs from analysis where the estimated accuracy of imputation was low ($r^2<0.3$).

Functional studies and *in silico* analysis of publicly available datasets

We performed the following assays for each gene in the one megabase region centered on the most significant SNP at the 17q21.31 locus (see Supplementary Methods): gene expression analysis in EOC cell lines (n=51) compared to normal cell lines from ovarian cancer precursor tissues (OCPTs)[56], including ovarian surface epithelial cells (OSECs) and fallopian tube secretory epithelial cells (FTSECs) (n=73), and CpG island methylation analysis in high grade serous ovarian cancer (HGS-EOC) tissues (n=106) and normal tissues (n=7). Genes in the region were also evaluated *in silico* by mining publicly available molecular data generated for primary EOCs and other cancer types, including The Cancer Genome Atlas (TCGA) analysis of 568 HGS EOCs[18], the Gene Expression Omnibus series GSE18520 dataset of 53 HGS EOCs [19], and the Catalogue Of Somatic Mutations In Cancer (COSMIC) database[20].

We used these data to 1) compare gene expression between a) EOC cell lines and normal cell lines and b) tumor tissue and normal tissue from TCGA, 2) compare gene methylation status in HGS-EOCs and normal tissue, 3) conduct gene expression quantitative trait locus (eQTL) analyses to evaluate genotype-gene expression associations in normal OCPTs, lymphoblastoid cells, and HGS-EOCs, and 4) conduct methylation quantitative trait locus (mQTL) analyses in HGS-EOCs to evaluate genotype-gene methylation associations. Data from ENCyclopedia Of DNA Elements (ENCODE) [57] were used to evaluate the overlap between regulatory elements in non-coding regions and risk-associated SNPs. ENCODE describes regulatory DNA elements (e.g. enhancers, insulators and promotors) and non-coding RNAs (e.g. miRNAs, long non-coding and piwi-interacting RNAs) that may be targets for susceptibility alleles. However, ENCODE does not include data for EOC associated tissues, and activity of such regulatory elements often varies in a tissue specific

manner [57,58]. Therefore, we profiled the spectrum of non-coding regulatory elements in OSECs and FTSECs using a combination of formaldehyde assisted isolation of regulatory elements sequencing (FAIRE-seq) and RNA sequencing (RNA-seq) (Supplementary Methods).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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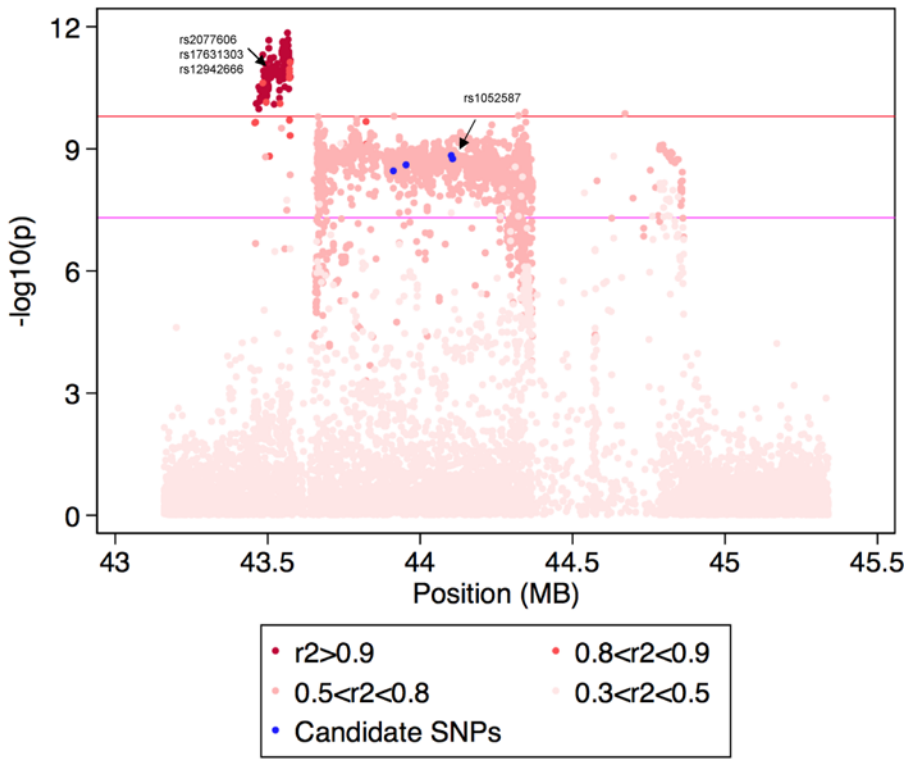

Figure 1. Regional association plot for genotyped and imputed SNPs at 17q21.31

The middle portion of the plot contains the region of the inversion polymorphism (ch 17: 43,624,578-44,525,051, hg build 37), with the four blue dots representing the candidate miRSNPs (rs4640231, rs1052587, and rs17574361) and the tagSNP, rs916793. rs1052587 in the 3′UTR of *MAPT* has the strongest signal ($P=4.6\times10^{-8}$) among the miRSNPs. The cluster on the left side of the plot (around 43.5 MB) contains highly correlated SNPs ($r^2=0.99$), including three directly genotyped intronic SNPs, rs2077606 and rs17631303 in *PLEKHM1* ($P=3.9\times10^{-10}$ and $P=4.7\times10^{-10}$, respectively), and rs12942666 in ARHGAP27 ($P=1.0\times10^{-9}$). The linkage disequilibrium between each plotted SNP and the top-ranked SNP in the region with the best clustering, rs12942666, is depicted by the color scheme; the deeper the color red, the stronger the correlation between the plotted SNP and rs12942666. The top miRSNP, rs1052587, is moderately correlated ($r^2=0.76$) with rs2077606, rs17631303, and rs12942666 in our study population. (n=8,371 invasive serous cases and n= 23,491 controls, of European ancestry).

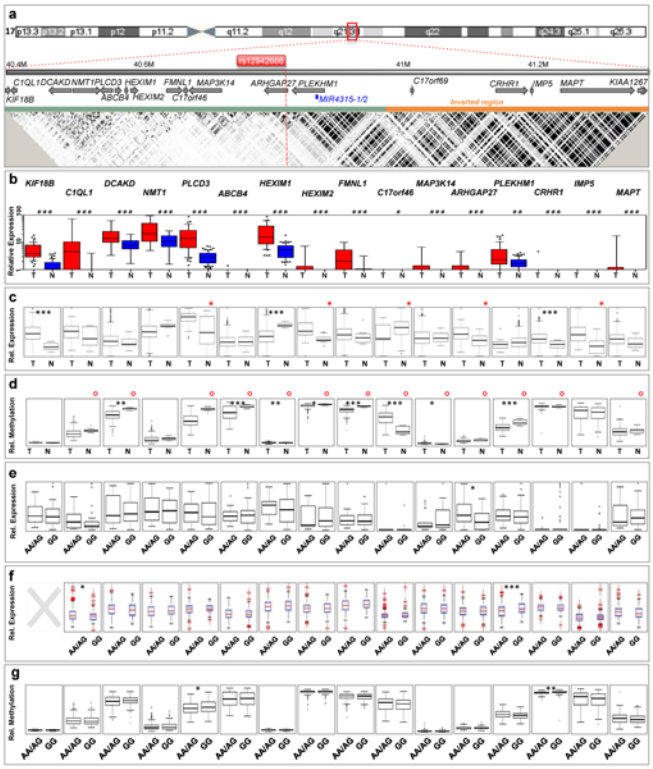

Figure 2. Expression and methylation analyses at the 17q21.31 ovarian cancer susceptibility locus

(a) Genomic map and LD structure. The location and approximate size of 17 known protein coding genes (grey) and one microRNA (blue) in the region are shown relative to the location of rs12942666. Orange indicates the location of the inversion polymorphism, and green indicates the region outside the inversion.

(b) Gene expression (EOC and normal cell lines). Gene expression analysis in Epithelial Ovarian Cancer (EOC) cell lines (T; n=51) compared to normal ovarian surface epithelial cells (OSECs) and fallopian tube secretory epithelial cells (FTSEC) (N; n=73) (* $p<0.05$, ** $p<0.01$, *** $p<0.001$).

(c) Gene expression (Primary EOCs and Normal Tissue). Boxplots of The Cancer Genome Atlas (TCGA) Affymetrix U133A-array based gene expression in primary high-grade serous ovarian tumors (T; n=568) and normal fallopian tube tissues (N; n=8). Where data were not available in TCGA, gene expression data from the Gene Expression Omnibus series GSE18520 dataset containing 53 high-grade serous tumors and 10 normal ovarian tissues are shown (indicated by a red asterisk).

(d) Methylation (Primary Tumors and Normal Tissue). Methylation analysis of 106 high-grade serous ovarian tumors compared to normal ovarian tissues (n=7). Methylation data were generated for CpG site(s) associated with each gene using the Illumina 450 methylation array. Pairwise analysis of methylation for an individual CpG for each gene is based on the CpG with most significant inverse relationship to gene expression (i.e. cis negative), for a subset of 43 tumors having available gene expression data. Statistically significant cis-negative probes are indicated by a red open circle.

(e) Expression quantitative trait locus (eQTL) analysis (OSECs/FTSECs). eQTL analysis comparing expression for each gene to genotype for the most statistically significant SNP at 17q21.31 (rs12942666), for 73 normal OSEC/FTSEC lines. Data are presented as box plots comparing expression levels in cases carrying rare homozygotes/heterozygotes, with cases homozygous for the common allele.

(f) Expression quantitative trait locus (eQTL) analysis (Primary EOCs). eQTL analysis comparing expression for each gene to genotype using level 3 gene expression profiling data from Agilent 244K custom arrays and level 2 genotype data from the Illumina 1M-Duo BeadChip for 568 high-grade serous ovarian cancer patients from TCGA. In all panels * $p<0.05$, ** $p<0.01$, *** $p<0.001$. Grey X's indicate data not available. Here, genotype data for rs2077606 is used (rather than rs12942666) because rs12942666 was not genotyped in the TCGA dataset.

(g) Methylation quantitative trait locus (mQTL) analysis (Primary EOCs). mQTL analysis showing methylation status in 227 high-grade serous EOCs relative to rs12942666 genotype.

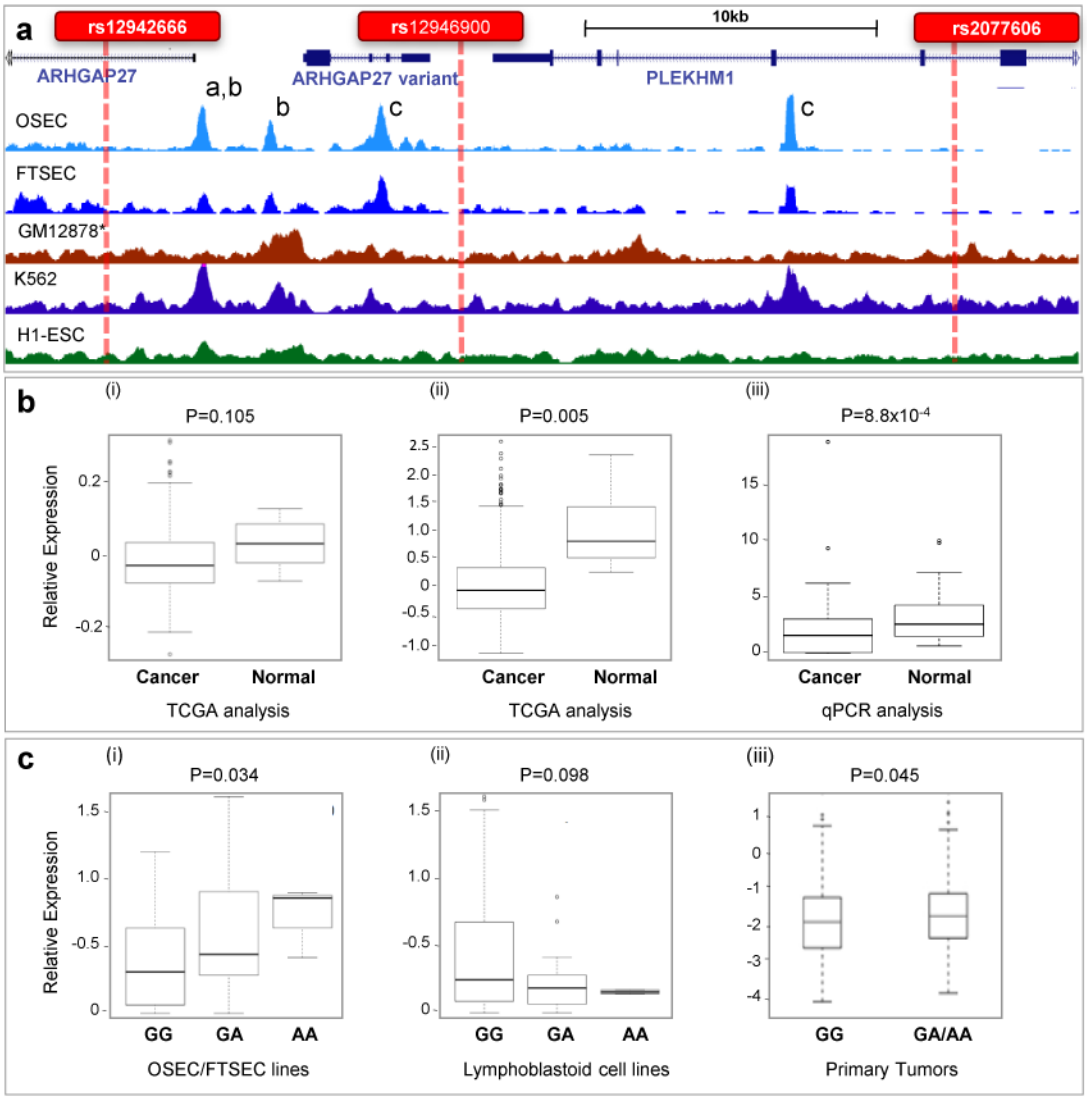

Figure 3. eQTL associations between the rs2077606 susceptibility SNP at 17q21

(a) Analysis of the chromatin landscape at *ARHGAP27* and *PLEKHM1* in normal ovarian surface epithelial and fallopian tube secretory epithelial cells (OSECs/FTSECs) by formaldehyde assisted isolation of regulatory elements sequencing (FAIRE-seq). Alignment with ENCODE FAIRE-seq tracks (shown) and ChIP-seq tracks (not shown) from non-EOC related cell lines reveals open chromatin peaks corresponding to (a) promoters (b) CTCF insulator binding sites and (c) H3K4me3 signals, suggestive of a dynamic regulatory region. An H3K4me3 signal at a coding *ARHGAP27* mRNA variant (c) located between the genes is highly pronounced in OSEC/FTSEC, suggesting tissue-specific expression and function. Several of the top-ranking SNPs fall within transcription factor binding sites (TFFS) (Supplementary Table S2). rs12942666 did not coincide with TFBS, but tightly linked SNPs, rs12946900 and rs2077606 fell within predicted binding sites for SPIB and ZEB1, respectively.

(b) We analyzed the expression of *SPIB* and *ZEB1* in primary high-grade serous tumors from TCGA and found (i) no significant change in SPIB expression but (ii) significant down-regulation of *ZEB1* in tumors compared to normal tissues. (iii) QPCR analysis of *ZEB1* expression in 73 OCPT and 50 EOC cell lines replicated the finding that *ZEB1*

expression is lower in cancer cell lines compared to normal precursor tissues. (c) eQTL analysis in OSECs/FTSECs for different alleles of rs2077606. There was a (i) significant eQTL for *ARHGAP27*, with the minor (A) allele being associated with increased *ARHGAP27* expression (P=0.034), (ii) no evidence of an association between rs2077606 genotypes and *ARHGAP27* expression in lymphoblastoid cell lines suggesting this association may be tissue-specific. (iii) We observed a borderline significant eQTL association between *ZEB1* mRNA and rs2077606 in tumors from TCGA, with the minor risk allele also associated with lower expression.

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Table 1

Tests of association by histological subtype for directly genotyped and imputed SNPs at 17q21.31 most strongly associated with invasive epithelial ovarian cancer risk among Europeans

SNP Major>minor allele allele	Coordinate[a]	MAF	Subtype	Number of cases (versus 23,491 controls)	Per-allele OR (95% CI)[b]	P-value
rs1052587[c] (T>C)	44102604	0.22	All Invasives	14,533	1.10 (1.06-1.13)	1.9×10^{-7}
			Serous	8,371	1.12 (1.08-1.17)	4.6×10^{-8}
			Endometrioid	2,068	1.11 (1.04-1.19)	5.2×10^{-3}
			Clear Cell	1,025	0.98 (0.88-1.09)	0.68
			Mucinous	944	1.07 (0.96-1.20)	0.22
rs12942666[d] (A>G)	43499839	0.22	All Invasives	14,533	1.11 (1.07-1.15)	3.3×10^{-8}
			Serous	8,371	1.15 (1.11-1.20)	1.0×10^{-9}
			Endometrioid	2,068	1.10 (1.02-1.18)	0.04
			Clear Cell	1,025	1.04 (0.92-1.14)	0.61
			Mucinous	944	1.04 (0.92-1.16)	0.55
rs2960000[e] (T>C)	43534353	0.18	All Invasives	14,533	1.12 (1.08-1.16)	4.2×10^{-9}
			Serous	8,371	1.16 (1.12-1.20)	3.3×10^{-10}
			Endometrioid	2,068	1.12 (1.03-1.20)	0.01
			Clear Cell	1,025	1.05 (0.93-1.16)	0.44
			Mucinous	944	1.03 (0.90-1.15)	0.65

Abbreviations: MAF=minor allele frequency in controls; OR=Odds ratio; CI=Confidence intervals

[a] Genome build NCBI B37/human genome build 19 assembly.

[b] OR and 95% CI per copy of the minor allele, with adjustment for the first five eigenvalues from principal components analysis.

[c] rs1052587 is the most statistically significant miRNA binding site SNP among all invasives and serous; it resides in a putative miRNA binding site between microtubule-associated protein tau (*MAPT*) and miR- 34a-5p (chr 1:9134225-9134425).

[d] rs12942666 is a SNP at 17q21.31 that was directly genotyped as part of COGs; it is in strong linkage disequilibrium (r^2=0.99) with two other 17q21.31 SNPs that were directly genotyped but had less optimal clustering: rs2077606 (P=3.9×10^{-10} for the serous subtype) and rs17631303 (P=4.7×10^{-10} for the serous subtype).

[e] rs2960000 represents the most statistically significant SNP at 17q21.31 (among all invasives) that was imputed from the 1000 genome Project reference panel with an R-squared quality metric of 95% or greater (http://www.1000genomes.org/page.php).

nature genetics

Identification of six new susceptibility loci for invasive epithelial ovarian cancer

Genome-wide association studies (GWAS) have identified 12 epithelial ovarian cancer (EOC) susceptibility alleles. The pattern of association at these loci is consistent in *BRCA1* and *BRCA2* mutation carriers who are at high risk of EOC. After imputation to 1000 Genomes Project data, we assessed associations of 11 million genetic variants with EOC risk from 15,437 cases unselected for family history and 30,845 controls and from 15,252 *BRCA1* mutation carriers and 8,211 *BRCA2* mutation carriers (3,096 with ovarian cancer), and we combined the results in a meta-analysis. This new study design yielded increased statistical power, leading to the discovery of six new EOC susceptibility loci. Variants at 1p36 (nearest gene, *WNT4*), 4q26 (*SYNPO2*), 9q34.2 (*ABO*) and 17q11.2 (*ATAD5*) were associated with EOC risk, and at 1p34.3 (*RSPO1*) and 6p22.1 (*GPX6*) variants were specifically associated with the serous EOC subtype, all with $P < 5 \times 10^{-8}$. Incorporating these variants into risk assessment tools will improve clinical risk predictions for *BRCA1* and *BRCA2* mutation carriers.

The risk of developing invasive EOC is higher than the population average for relatives of women diagnosed with the disease[1,2], indicating the importance of genetic factors in disease susceptibility. Approximately 25% of the familial aggregation of EOC is explained by rare, high-penetrance alleles of *BRCA1* and *BRCA2* (ref. 3). Furthermore, population-based GWAS have identified common variants associated with invasive EOC at 11 loci[4–9], but only 6 have also been evaluated in *BRCA1* and/or *BRCA2* mutation carriers. All loci analyzed displayed associations in mutation carriers that were consistent with the associations observed in the general population[10–12]. In addition, the 4q32.3 locus is associated with EOC risk for *BRCA1* mutation carriers only[13]. However, the common genetic variants identified explain less than 3.1% of the excess familial risk of EOC, so additional susceptibility loci are likely to exist.

Women diagnosed with EOC and unaffected women from the general population ascertained through the Ovarian Cancer Association Consortium (OCAC)[14] and *BRCA1* and *BRCA2* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA)[15] were genotyped as part of the Collaborative Oncological Gene-environment Study (COGS) using the iCOGS custom array. In addition, data were available for cases and controls from three EOC GWAS. We first evaluated whether the EOC susceptibility loci at 8q21.13, 10p12.31, 17q12, 5p15.33 and 17q21.31 recently identified by OCAC[7–9] also showed evidence of association in *BRCA1* and *BRCA2* mutation carriers. Using data from >200,000 genotyped SNPs[7,13,16], we performed imputation of common variants from 1000 Genomes Project data[17] and evaluated the associations of these SNPs with invasive EOC risk in OCAC samples and in *BRCA1* and *BRCA2* mutation carriers from CIMBA. Given the strong evidence for a significant overlap in loci predisposing to EOC in the general population and those associated with risk in *BRCA1* and *BRCA2* mutation carriers, we carried out a meta-analysis of the EOC risk associations to identify new EOC susceptibility loci.

Genotype data were available for imputation on 15,252 *BRCA1* mutation carriers and 8,211 *BRCA2* mutation carriers, of whom 2,462 and 631, respectively, were affected with EOC[13,16]. For OCAC samples, genotyping data were available from 15,437 women with invasive EOC (including 9,627 with serous EOC) and 30,845 controls from the general population[7]. Imputation was performed separately for *BRCA1* mutation carriers, *BRCA2* mutation carriers, OCAC-COGS samples and samples included in the three OCAC GWAS (**Supplementary Figs. 1** and **2**, and **Supplementary Tables 1** and **2**). The meta-analysis was based on data for 11,403,952 SNPs (**Supplementary Fig. 3**).

Of the five EOC susceptibility loci that had not yet been evaluated in mutation carriers, two were associated with EOC risk for both *BRCA1* and *BRCA2* mutation carriers at $P < 0.05$ (10p12.31 and 17q21.31) (**Supplementary Table 3**). Overall, 7 of the 12 known EOC susceptibility loci provided evidence of association in *BRCA1* mutation carriers and 6 were associated in *BRCA2* mutation carriers. With the exception of 5p15.33 (*TERT*), all loci had hazard ratio (HR) estimates in *BRCA1* and *BRCA2* mutation carriers that were in the same direction as the odds ratio (OR) estimates for the serous subtype EOC samples in OCAC (**Fig. 1**). Analyzing the associations jointly in *BRCA1* and *BRCA2* mutation carriers and serous EOC cases in OCAC provided stronger evidence of association, with smaller *P* values for eight of the susceptibility variants in comparison to the analysis in OCAC samples alone.

Using the imputed genotypes, we observed no new associations at $P < 5 \times 10^{-8}$ in the analysis of associations in *BRCA1* and *BRCA2* mutation carriers separately. However, we identified seven previously unreported associations ($P < 5 \times 10^{-8}$) in OCAC samples alone, in the meta-analysis of EOC associations in *BRCA1* and *BRCA2* mutation carriers and OCAC samples, or in the meta-analysis in *BRCA1* and *BRCA2* mutation carriers and serous EOC cases from OCAC (**Supplementary Fig. 4** and **Supplementary Tables 4** and **5**). SNPs in six of these loci remained genome-wide statistically significant after we reimputed genotypes with imputation parameters set to

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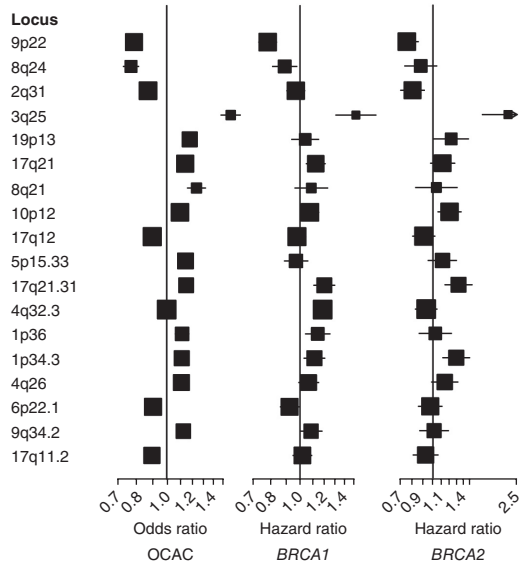

Figure 1 HR estimates for association with EOC of 12 previously reported EOC susceptibility variants and the 6 new susceptibility variants for OCAC samples, *BRCA1* mutation carriers and *BRCA2* mutation carriers. Error bars indicate 95% confidence intervals. The arrow indicates that the confidence interval extends beyond the scale of the *x* axis.

maximize accuracy (**Fig. 1** and **Table 1**). We found SNPs at 17q11.2 (near *ATAD5*) to be associated with invasive EOC in the OCAC samples ($P < 5 \times 10^{-8}$) (**Table 1**). For the lead SNP, chr17:29181220:I, the estimated HR value for *BRCA1* mutation carriers was significantly different from the estimate in OCAC samples ($P = 0.005$); the association for *BRCA2* mutation carriers was consistent with the OCAC OR estimate (*BRCA2*-OCAC meta-analysis $P = 2.6 \times 10^{-9}$). SNPs at four loci were associated at $P < 5 \times 10^{-8}$ with risk of all invasive EOC subtypes in the meta-analysis (**Supplementary Fig. 5**): 1p36, 1p34.3, 4q26 and 9q34.2. At 1p34.3, the most strongly associated SNP, rs58722170, displayed stronger associations in the meta-analysis of serous EOC cases from OCAC ($P = 2.7 \times 10^{-12}$). In addition, SNPs at 6p22.1 were associated at a genome-wide significance level in the meta-analysis of associations with serous EOC ($P = 3.0 \times 10^{-8}$) but not in the meta-analysis of all invasive EOC associations ($P = 6.8 \times 10^{-6}$).

The most significantly associated SNP at each of the six new loci had high imputation accuracy ($r^2 \geq 0.83$). At the 1p34.3, 1p36 and 6p22.1 loci, there was at least one genome-wide significant genotyped SNP correlated with the lead SNP (pairwise $r^2 \geq 0.73$) (**Supplementary Fig. 5**, **Supplementary Table 6** and **Supplementary Note**). We genotyped the leading (imputed) SNPs of the three other loci in a subset of the samples using iPLEX technology (**Supplementary Note**). Correlations between the expected allele dosages from imputation and the observed genotypes for the variants at 4q26 and 9q34.2 ($r^2 = 0.90$ and 0.84, respectively) were consistent with the estimated imputation accuracy scores (0.93 and 0.83 for CIMBA samples). The lead SNP at 17q11.2 failed iPLEX design. However, the risk-associated allele was highly correlated with the AA haplotype of two genotyped variants on the iCOGS array (rs9910051 and rs3764419). This haplotype was strongly associated with ovarian cancer risk in the subset of samples genotyped using the iCOGS array (*BRCA2*-OCAC meta-analysis $P = 8.6 \times 10^{-8}$ for this haplotype and $P = 1.8 \times 10^{-8}$ for chr17:29181220:I) (**Supplementary Table 7**).

None of the regions contained additional SNPs that displayed EOC associations at $P < 1 \times 10^{-4}$ in OCAC samples, *BRCA1* mutation carriers or *BRCA2* mutation carriers in multi-variable analyses adjusted

Table 1 Association test results for loci associated at $P < 5 \times 10^{-8}$ in the second imputation stage

						OCAC all histologies			OCAC serous			*BRCA1* mutation carriers			*BRCA2* mutation carriers			Meta-analysis all histologies[b]	Meta-analysis serous[c]
Locus	Nearest gene	rs ID	Ref[g]	Eff[g]	EAF[h]	$r^{2\,a}$	OR (95% CI)	P	OR (95% CI)	P	$r^{2\,a}$	HR (95% CI)	P	$r^{2\,a}$	HR (95% CI)	P	P	P
1p36	*WNT4*	rs56318008	C	T	0.15	0.98	1.11 (1.07–1.16)	3.9×10^{-7}	1.12 (1.07–1.18)	$\mathbf{3.1 \times 10^{-6}}$	0.98	1.15 (1.05–1.26)	3.1×10^{-3}	0.98	1.03 (0.86–1.23)	0.74	7.6×10^{-9}	5.7×10^{-8}
1p34.3	*RSPO1*	rs58722170	G	C	0.23	0.85	1.08 (1.04–1.12)	9.7×10^{-5}	1.12 (1.08–1.18)	1.1×10^{-7}	0.83	1.14 (1.05–1.23)	1.5×10^{-3}	0.83	1.35 (1.17–1.57)	5.2×10^{-5}	1.6×10^{-8}	2.7×10^{-12}
4q26	*SYNPO2*	rs17329882	A	C	0.24	0.95	1.09 (1.06–1.13)	5.9×10^{-7}	1.11 (1.07–1.16)	6.4×10^{-7}	0.93	1.08 (1.00–1.17)	0.042	0.93	1.15 (1.00–1.33)	0.06	1.4×10^{-8}	1.6×10^{-8}
6p22.1	*GPX6*	rs116133110[e]	T	C	0.31	0.99	0.93 (0.91–0.97)	9.0×10^{-5}	0.91 (0.87–0.94)	2.6×10^{-7}	0.99	0.92 (0.86–0.99)	0.023	0.99	0.97 (0.85–1.10)	0.64	6.8×10^{-6}	3.0×10^{-8}
9q34.2	*ABO*	rs635634	C	T	0.19	0.85	1.11 (1.07–1.16)	1.1×10^{-7}	1.12 (1.08–1.18)	1.0×10^{-6}	0.83	1.11 (1.02–1.21)	0.012	0.83	1.05 (0.89–1.23)	0.55	4.4×10^{-9}	4.2×10^{-8}
17q11.2	*ATAD5*	chr17:29181220:I[f]	A	AT	0.28	0.95	0.91 (0.88–0.94)	5.4×10^{-9}	0.91 (0.87–0.94)	8.1×10^{-7}	0.94	1.01 (0.94–1.08)	0.88	0.93	0.92 (0.80–1.05)	0.23	$2.6 \times 10^{-9\,d}$	$3.9 \times 10^{-7\,d}$

Results are reported for ovarian cancer in *BRCA1* and *BRCA2* mutation carriers, for ovarian cancer as well as the serous subtype of ovarian cancer in OCAC, for the meta-analysis for ovarian cancer, and for the meta-analysis for all tumor histologies in *BRCA1* and *BRCA2* mutation carriers and serous ovarian cancer cases in OCAC. The SNP with the smallest *P* value is reported for each locus.
[a]Imputation accuracy r^2 estimate. [b]*P* value from the meta-analysis association test for ovarian cancer in OCAC samples and *BRCA1* and *BRCA2* mutation carriers. [c]*P* value from the meta-analysis association test for ovarian cancer in *BRCA1* and *BRCA2* mutation carriers and serous ovarian cancer in OCAC samples. [d]Meta-analysis of ovarian cancer associations in *BRCA2* mutation carriers and OCAC samples only. [e]rs116133110 is listed as rs6456822 in dbSNP. [f]chr17:29181220:I is listed as rs199661266 in dbSNP. [g]Reference and effect alleles. [h]Effect allele frequency.

Table 2 Associations with ovarian cancer subtypes in OCAC samples for loci associated with ovarian cancer at $P < 5 \times 10^{-8}$ in the meta-analysis

		All histologies		Serous		Endometrioid		Clear cell		Mucinous		
Locus	rs ID	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	P_{het}[a]
1p36	rs56318008	1.11 (1.06–1.15)	8×10^{-7}	1.12 (1.06–1.17)	6×10^{-6}	1.09 (1.00–1.19)	0.05	1.24 (1.10–1.39	5×10^{-4}	1.03 (0.91–1.17)	0.65	0.22
1p34.3	rs58722170	1.07 (1.03–1.11)	2×10^{-4}	1.12 (1.07–1.17)	4×10^{-7}	0.94 (0.87–1.02)	0.16	1.00 (0.89–1.12)	0.98	1.08 (0.97–1.21)	0.17	0.001
4q26	rs17329882	1.09 (1.06–1.13)	3×10^{-7}	1.11 (1.07–1.16)	3×10^{-7}	1.09 (1.01–1.18)	0.020	1.06 (0.96–1.18)	0.26	1.11 (0.99–1.23)	0.06	0.88
6p22.1	rs116133110	0.94 (0.91–0.97)	9×10^{-5}	0.91 (0.87–0.94)	3×10^{-7}	0.95 (0.89–1.02)	0.16	1.05 (0.95–1.15)	0.34	1.03 (0.94–1.14)	0.53	0.008
9q34.2	rs635634	1.12 (1.08–1.16)	9×10^{-9}	1.13 (1.08–1.18)	2×10^{-7}	1.12 (1.03–1.21)	0.007	1.03 (0.92–1.16)	0.58	1.23 (1.10–1.38)	3×10^{-4}	0.23
17q11.2	chr17:29181 220:I	0.90 (0.87–0.93)	1×10^{-9}	0.90 (0.87–0.94)	2×10^{-7}	0.88 (0.82–0.95)	5×10^{-4}	0.88 (0.80–0.98)	0.020	1.01 (0.91–1.12)	0.84	0.18

[a]*P* value for the heterogeneity in associations with different tumor subtypes.

for the lead SNP in each region, indicating that they each contain only one independent set of correlated, highly associated variants (iCHAVs). Relative to 1000 Genomes Project data, we had genotyped or imputed data covering 91% of the genetic variation at 1p36, 84% of the variation at 1p34.3 and 83% of the variation at 4q26. The other three new loci had coverage of less than 80% (**Supplementary Note**). There was evidence for heterogeneity at $P < 0.05$ in the associations with histological subtype in OCAC samples for the lead SNPs at 1p34.4 and 6p22.1 but not for the lead SNPs at 1p36, 4q26, 9q34.2 and 17q11.2 (**Table 2**).

We carried out a competing risks association analysis in *BRCA1* and *BRCA2* mutation carriers to investigate whether these loci were also associated with breast cancer risk for mutation carriers (**Supplementary Note**). We used the most strongly associated genotyped SNPs for this purpose because the statistical method required actual genotypes[18]. The HR estimates for EOC were consistent with the estimates from the main analysis for all SNPs (**Supplementary Table 8**). None of the SNPs displayed associations with breast cancer risk at $P < 0.05$.

At each of the six loci, we identified a set of SNPs with odds of less than 100 to 1 against them being the causal variant; most were in non-coding DNA regions (**Supplementary Table 9**). None were predicted to have likely deleterious functional effects, although some were in or near chromatin biofeatures in fallopian tube and ovarian epithelial cells, which might represent the functional regulatory targets of the risk-associated SNPs (**Table 3** and **Supplementary Table 10**). We also evaluated the protein-coding genes in each region for their role in EOC development and as candidate susceptibility gene targets. Molecular profiling data from 496 high-grade serous ovarian cancers (HGSOCs) collected by The Cancer Genome Atlas (TCGA) indicated frequent loss or deletion at 4 risk loci (1p36, 4q26, 9q34.2 and 17q11.2) (**Supplementary Table 11**). Consistent with this observation, the expression of *WNT4*, *SYNPO2* and *ABO* was significantly downregulated in ovarian tumors, whereas *ATAD5* expression was upregulated ($P < 6 \times 10^{-5}$, HuEx platform). Somatic coding-sequence mutations in the six genes nearest the index SNPs were rare. We performed expression quantitative trait locus (eQTL) analysis in a series of 59 normal ovarian tissues (**Supplementary Table 12**) to evaluate the gene nearest the top ranked SNP at each locus. For the five genes expressed in normal cells, we found no statistically significant eQTL associations for any of the putative causal SNPs at each locus; neither did we find any significant tumor-eQTL associations for these genes based on data from TCGA (**Supplementary Table 12**). At the 1p36 locus, the most strongly associated variant, rs56318008, was located

Table 3 Summary of data on SNPs, closest gene and all genes in a 1-Mb region for each locus

Loci	Position of top SNP	Number of putatively causal SNPs	Genes in window of putatively causal SNP	Number of SNPs aligned with biofeatures	Normal eQTL closest gene	Tumor DNA copy number	Significant expression difference in tumor versus normal[c]	Known role of gene in cancer	Number of genes in 1-Mb region	Other known cancer genes in 1-Mb region
1p36	Promoter region of *WNT4*	39	*WNT4*, *CDC42*, *LINC00339*	11	NS	Loss	Down	Yes	11	*RAP1GAP*, *CDC42*
1p34.3	Intron 3 of *RSPO1*	15	*RSPO1*	0	NS	Gain		Yes	22	*C1orf109*, *FHL3*
4q26	Intron 3 of *SYNPO2*	4	*SYNPO2*	2	NS[b]	Loss	Down	Yes	12	None
6p22.1	Intron 1 of *GPX6*	22	*GPX6*, *GPX5*	1	NA	Gain			23	*ZKSCAN3*, *TRIM27*
9q34.2	4.3 kb upstream of *ABO*	18	*ABO*, *SLC2A6*[a]	1	NS	Loss	Down	Yes	32	*TSC1*, *RALGDS*, *RPL7A*, *VAV2*
17q11.2	Intron 6 of *ATAD5*	16	*ATAD5*, *TEFM*, *ADAP2*, *CRLF3*, *SUZ12P1*	0	NS	Loss	Up	Yes	17	*NF1*

Proximal promoter regions were defined as the regions 1 kb upstream of the transcription start site. NA indicates no expression of *GPX6* in normal tissues. NS, not significant. Biofeatures are defined as open chromatin H3K4me3 or H3K27ac marks detected in normal ovarian and/or fallopian tube cells.
[a]There are 16 genes in this region—*ABO*, *SURF6*, *MED22*, *RPL7A*, *SNORD24*, *SNORD36B*, *SNORD36A*, *SNORD36C*, *SURF1*, *SURF2*, *SURF4*, *C9orf96*, *REXO4*, *ADAMTS13*, *CACFD1* and *SLC2A6*; however, all SNPs are within or upstream of *ABO* or upstream of *SLC2A6*. [b]Trend $P = 0.067$. [c]$P < 6 \times 10^{-5}$ with the HuEx platform.

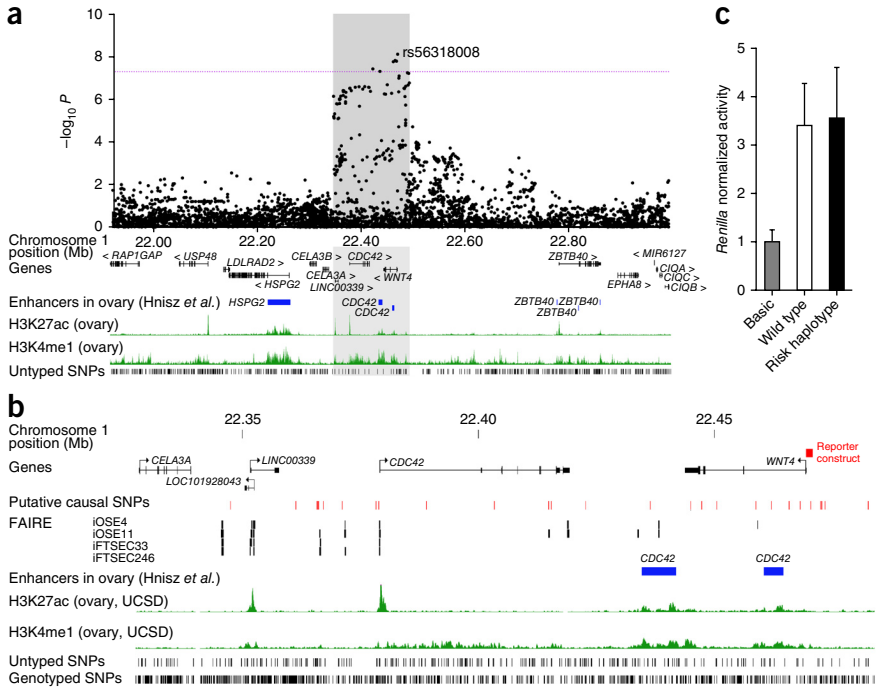

Figure 2 The 1p36 EOC susceptibility locus. (**a**) The Manhattan plot depicts the strength of association between all imputed and genotyped SNPs across the region bound by hg19 coordinates chr. 1: 21,922,893–22,991,643. The dotted line represents the genome-wide significance level of 5×10^{-8}. Additional tracks show genes and enhancers in the ovary as described in Hnisz *et al.*[38]. Positions of SNPs for which imputation $r^2 < 0.3$ and/or minor allele frequency (MAF) < 0.005 are shown in the bottom track as 'untyped' SNPs. H3K27ac, acetylation of histone H3 at lysine 27; H3K4me1, monomethylation of histone H3 at lysine 4. (**b**) The shaded iCHAV region from **a** is shown, depicting the genes and the location of the *WNT4* promoter construct as a red box. Red ticks show the positions of the putative causal variants following likelihood ratio testing. Signals from formaldehyde-assisted regulatory element sequencing (FAIRE-seq) data derived from ovarian cells are represented by black marks, and the locations of predicted *CDC42* enhancers[38] are represented by blue boxes. The positions of genotyped SNPs and those that were neither genotyped nor well imputed ('untyped') are shown. (**c**) Normalized luciferase reporter activity following triplicate transfections of wild-type and risk haplotype *WNT4* promoter constructs in iOSE4 cells. Error bars represent the s.e.m. from three independent experiments.

in the promoter region of *WNT4*, which encodes a ligand in the WNT signal transduction pathway, critical for cell proliferation and differentiation. Using a luciferase reporter assay, we found no effect of these putatively causal SNPs on *WNT4* transcription in iOSE4 normal ovarian cells (**Fig. 2**). Some of the putative causal SNPs at 1p36 were located in *CDC42* and *LINC00339*, and several were in putative regulatory domains in ovarian tissues (**Fig. 2** and **Supplementary Table 10**). *CDC42* is known to have a role in migration and signaling in ovarian and breast cancers[19,20]. SNPs at 1p36 are also associated with increased risk of endometriosis, and *WNT4*, *CDC42* and *LINC00339* have all been implicated in endometriosis[21], a known risk factor for endometrioid and clear cell EOCs[22].

The strongest associated variant at 1q34, rs58722170, was located in *RSPO1*, which encodes R-spondin 1, a protein involved in cell proliferation (**Supplementary Fig. 6**). RSPO1 is important in tumorigenesis and early ovarian development[23,24], and it regulates *WNT4* expression in the ovaries[25]. *SYNPO2* at 4q26 encodes myopodin, which is involved in cell motility and growth[26] and has a reported tumor-suppressor role[27–30]. rs635634 is located upstream of the *ABO* gene (**Supplementary Fig. 7**). A moderately correlated variant (rs505922; $r^2 = 0.52$) determines ABO blood group and is associated with increased risk of pancreatic cancer[31,32]. Previous studies in OCAC also showed a modestly increased risk of EOC for individuals with the A blood group[33]. The moderate correlation between rs635634 and rs505922 and the considerably weaker EOC association of rs505922 ($P = 1.2 \times 10^{-5}$) suggest that the association with blood group is probably not driving the risk association. The indel chr17:29181220:I at 17q11.2 is located in *ATAD5*, which acts as a tumor-suppressor gene[34–36] (**Supplementary Fig. 8**). ATAD5 protein modulates the interaction between RAD9A and BCL2 to induce DNA damage–related apoptosis. Finally, rs116133110, at 6p22.1, lies in *GPX6*, which has no known role in cancer.

The 6 new loci reported in this study increase the number of genome-wide significant common variant loci so far identified for EOC to 18. Taken together, these loci explain approximately 3.9% of the excess familial relative risk of EOC in the general population and account for approximately 5.2% of the polygenic modifying variance for EOC in *BRCA1* mutation carriers and 9.3% of the variance in *BRCA2* mutation carriers. The similarity in the magnitude of the associations between *BRCA1* and *BRCA2* mutation carriers and cases from population-based studies suggests a general model of susceptibility whereby *BRCA1* and *BRCA2* mutations and common alleles interact multiplicatively on the relative risk scale for EOC[37]. This model predicts large differences in absolute EOC risk between individuals carrying many risk-associated alleles and individuals carrying few alleles for EOC susceptibility in *BRCA1* and *BRCA2* mutation carriers[13,16]. Incorporating EOC susceptibility variants into risk assessment tools will improve risk prediction and might be particularly useful for *BRCA1* and *BRCA2* mutation carriers.

URLs. Nature Publishing Group, *Nature Genetics*–iCOGS, http://www.nature.com/icogs/; The Cancer Genome Atlas (TCGA) Project, http://cancergenome.nih.gov/; cBio Cancer Genomics Portal, http://www.cbioportal.org/; Pupasuite 3.1, http://pupasuite.bioinfo.cipf.es/; CIMBA quality control guidelines, http://ccge.medschl.cam.ac.uk/consortia/cimba/members/data%20management/CIMBA%20and%20BCAC%20Quality%20Control%20November%202008%20v2.doc; R software, http://www.r-project.org/.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

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COMPETING FINANCIAL INTERESTS

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ONLINE METHODS

Study populations. We obtained data on *BRCA1* and *BRCA2* mutation carriers through CIMBA. Eligibility in CIMBA is restricted to females 18 years or older with pathogenic mutations in *BRCA1* or *BRCA2*. The majority of the participants were sampled through cancer genetics clinics[15], including some related participants. Fifty-four studies from 27 countries contributed data. After quality control, data were available on 15,252 *BRCA1* mutation carriers and 8,211 *BRCA2* mutation carriers, of whom 2,462 and 631, respectively, were affected with EOC (**Supplementary Table 1**).

Data were available for stage 1 of three population-based EOC GWAS. These included 2,165 cases and 2,564 controls from a GWAS from North America ('US GWAS')[39], 1,762 cases and 6,118 controls from a UK-based GWAS ('UK GWAS')[6], and 441 cases and 441 controls from the Mayo GWAS. Furthermore, 11,069 cases and 21,722 controls were genotyped using the iCOGS array ('OCAC-iCOGS' stage data). Overall, 43 studies from 11 countries provided data on 15,437 women diagnosed with invasive EOC, 9,627 of whom were diagnosed with serous EOC, and 30,845 controls from the general population.

All subjects included in this analysis were of European descent and provided written informed consent as well as data and blood samples under ethically approved protocols. Further details of the OCAC and CIMBA study populations as well as the genotyping, quality control and statistical analyses have been described elsewhere[7,13,16].

Genotype data. Genotyping and imputation details for each study are shown in **Supplementary Table 1**.

Confirmatory genotyping of imputed SNPs. To evaluate the accuracy of imputation for the SNPs we found to be associated with EOC risk, we genotyped rs17329882 (4q26) and rs635634 (9q34.2) in a subset of 3,541 subjects from CIMBA using Sequenon's iPLEX technology. The lead SNP at 17q11.2, chr17:29181220:I, failed iPLEX design. We performed quality control of the iPLEX data according to CIMBA guidelines. After quality control, we used the imputation results to generate the expected allele dosage for each genotyped sample and computed the Pearson product-moment correlation coefficient between the expected allele dosage and the observed genotype. The squared correlation coefficient was compared to the imputation accuracy as estimated from the imputation.

Quality control of GWAS and iCOGS genotyping data. We carried out quality control separately for *BRCA1* mutation carriers, *BRCA2* mutation carriers, the three OCAC GWAS and the OCAC-iCOGS samples, but quality criteria were mostly consistent across studies. We excluded samples if they were not of European ancestry, if they had a genotyping call rate of <95%, if they showed low or high heterozygosity, if they were not female or had ambiguous sex or if they were duplicates (cryptic or intended). In the OCAC studies, one individual was excluded from each pair of samples found to be first-degree relatives, and duplicate samples between the iCOGS stage and any of the GWAS were excluded from the iCOGS data. SNPs were excluded if they were monomorphic, had a call rate of < 95%, showed evidence of deviation from Hardy-Weinberg equilibrium or had low concordance between duplicate pairs. For the Mayo GWAS and the UK GWAS, we also excluded rare SNPs (MAF < 1% or allele count < 5, respectively). We visually inspected genotype cluster plots for all SNPs with association $P < 1 \times 10^{-5}$ from each of the newly identified loci. We used the R GenABEL library version 1.6.7 for quality control.

Genotype data were available for analysis from iCOGS for 199,526 SNPs in OCAC-iCOGS samples, 200,720 SNPs in *BRCA1* mutation carriers and 200,908 SNPs in *BRCA2* mutation carriers. After quality control, for the GWAS, data were available on 492,956 SNPs for the US GWAS, 543,529 SNPs for the UK GWAS and 1,587,051 SNPs for the Mayo GWAS (**Supplementary Table 2**).

Imputation. We performed imputation separately for *BRCA1* mutation carriers, *BRCA2* mutation carriers, OCAC-iCOGS samples and each of the OCAC GWAS. We imputed variants from 1000 Genomes Project data using the v3 April 2012 release[17] as the reference panel. For OCAC-iCOGS samples, the UK GWAS and the Mayo GWAS, imputation was based on the 1000 Genomes Project data with singleton sites removed. To improve computation efficiency, we initially used a two-step procedure, which involved pre-phasing in the first step and imputation of the phased data in the second step. We carried out pre-phasing using SHAPEIT software[40]. We used IMPUTE version 2 software for the subsequent imputation[41] for all studies with the exception of the US GWAS, for which the MACH algorithm implemented in Minimac software version 2012.8.15, MACH version 1.0.18, was used. To perform imputation, we divided the data into segments of approximately 5 Mb each. We excluded SNPs from the association analysis if their imputation accuracy was $r^2 < 0.3$, their MAF was <0.005 in *BRCA1* or *BRCA2* mutation carriers or their accuracy was $r^2 < 0.25$ in OCAC-iCOGS samples, the UK GWAS, the US GWAS or the Mayo GWAS.

We performed more accurate imputation for the regions around the new EOC loci from the joint analysis of the data from *BRCA1* and *BRCA2* mutation carriers and the general population (any SNP with association $P < 5 \times 10^{-8}$). The boundaries of these regions were set 500 kb away from any significantly associated SNP in the region. As in the first run, 1000 Genomes Project data v3 were used as the reference panel, and IMPUTE2 software was applied. However, for the second round of imputation, we imputed genotypes without pre-phasing to improve accuracy. To further increase imputation accuracy, we changed some of the default parameters in the imputation procedure. These included an increase in the MCMC iterations to 90 (out of which the first 15 were used as burn-in), an increase in the buffer region to 500 kb and an increase in the number of haplotypes used as templates when phasing observed genotypes to 100. These changes were applied consistently for all data sets.

Statistical analyses. *Association analyses in the unselected ovarian cancer cases and controls from OCAC.* We evaluated the association between genotype and disease using logistic regression by estimating the associations with each additional copy of the minor allele (log-additive models). The analysis was adjusted for study and for population substructure by including the eigenvectors of the first five ancestry-specific principal components as covariates in the model. We used the same approach to evaluate SNP associations with serous ovarian cancer after excluding all cases with any other or unknown tumor subtype. For imputed SNPs, we used expected dosages in the logistic regression model to estimate SNP effect sizes and *P* values. We carried out analyses separately for OCAC-iCOGS samples and the three GWAS and pooled data thereafter using a fixed-effects meta-analysis. We carried out the analysis of reimputed genotypes for putative new susceptibility loci jointly for the OCAC-iCOGS samples and the GWAS samples. All results are based on the combined data from iCOGS and the three GWAS. We used custom written software for the analysis.

Associations in BRCA1 and BRCA2 mutation carriers from CIMBA. We carried out the ovarian cancer association analyses separately for *BRCA1* and *BRCA2* mutation carriers. The primary analysis was carried out within a survival analysis framework, with time to ovarian cancer diagnosis as the endpoint. Mutation carriers were followed until the age of ovarian cancer diagnosis or risk-reducing salpingo-oophorectomy (RRSO) or to the age at last observation. Breast cancer diagnosis was not considered to be a censoring event. To account for the non-random sampling of *BRCA1* and *BRCA2* mutation carriers with respect to their disease status, we conducted the analyses by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotype[18]. We assessed the associations between genotype and risk of ovarian cancer using the 1-degree-of-freedom score test statistic based on retrospective likelihood[18,42]. To account for the non-independence among related individuals in the sample, we used an adjusted version of the score test statistic, which uses a kinship-adjusted variance of the score[43]. We evaluated associations between imputed genotypes and ovarian cancer risk using a version of the score test as described above but with the posterior genotype probabilities replacing the genotypes. All analyses were stratified by the country of origin of the samples.

We carried out retrospective likelihood analyses in CIMBA using custom written functions in Fortran and Python. The score test statistic was implemented in R version 3.0.1 (ref. 44).

We evaluated whether there was evidence for multiple independent association signals in the region around each newly identified locus by evaluating the associations of genetic variants in the region while adjusting for the SNP with the smallest meta-analysis *P* value in the

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respective region. This was done separately for *BRCA1* mutation carriers, *BRCA2* mutation carriers and OCAC samples.

For one of the new associations, it was not possible to confirm the imputation accuracy of the lead SNP chr17:29181220:I at 17q11.2 through genotyping. Therefore, we inferred two-allele haplotypes for rs9910051 and rs3764419, highly correlated with the lead SNP ($r^2 = 0.95$), using an in-house program. These variants were genotyped on the iCOGS array, and this analysis was therefore restricted to 14,733 ovarian cancer cases and 9,165 controls from OCAC-COGS and 8,185 *BRCA2* mutation carriers for whom genotypes were available for both variants based on iCOGS. The association between the AA haplotype and risk was tested using logistic regression in OCAC samples and using Cox regression in *BRCA2* mutation carriers.

Meta-analysis. We conducted a meta-analysis of the EOC associations in *BRCA1* mutation carriers, *BRCA2* mutation carriers and the general population for genotyped and imputed SNPs using an inverse variance approach assuming fixed effects. We combined the logarithm of the per-allele HR estimate for the association with EOC risk in *BRCA1* and *BRCA2* mutation carriers and the logarithm of the per-allele OR estimate for the association with disease status in OCAC. For associations in *BRCA1* and *BRCA2* carriers, we used the kinship-adjusted variance estimator[43], which allows for the inclusion of related individuals in the analysis. We only used SNPs with results in OCAC and in at least one of the *BRCA1* or the *BRCA2* analyses. We carried out two separate meta-analyses, one for the associations with EOC in *BRCA1* mutation carriers, *BRCA2* mutation carriers and EOC samples in OCAC, irrespective of tumor histological subtype, and a second using only the associations with serous EOC in OCAC samples. The number of *BRCA1* and *BRCA2* mutation carriers with tumor histology information was too small to allow for subgroup analyses. However, previous studies have demonstrated that the majority of EOCs in *BRCA1* and *BRCA2* mutation carriers are high-grade serous[45–49]. Meta-analyses were carried out using Metal software, 2011-03-25 release[50].

Candidate causal SNPs in each susceptibility region. To identify a set of potentially causal variants, we excluded SNPs with a likelihood of being causal of less than 1:100, by comparing the likelihood of each SNP from the association analysis with the likelihood of the most strongly associated SNPs[51]. The remaining variants were then analyzed using Pupasuite 3.1 to identify potentially functional variants[52,53] (**Supplementary Table 9**).

Functional analysis. *Expression quantitative trait locus analysis in normal ovarian and fallopian tube cells.* Early-passage primary normal ovarian surface epithelial cells (OSECs) and fallopian tube epithelial cells were collected from disease-free ovaries and fallopian tubes. Normal ovarian epithelial cells were collected by brushing the surface of the ovary with a sterile cytobrush and were cultured in NOSE-CM[54]. Fallopian tube epithelial cells were collected by Pronase digestion as previously described[55], plated onto collagen-coated plastics (Sigma) and cultured in DMEM/F12 (Sigma-Aldrich) supplemented with 2% Ultroser G (BioSepra) and 1× penicillin-streptomycin (Lonza). By the time of RNA isolation, the fallopian tube cultures tested consisted of PAX8-positive fallopian tube secretory epithelial cells (FTSECs), consistent with previous observations that ciliated epithelial cells from the fallopian tube do not proliferate *in vitro*. Cell lines were routinely tested for mycoplasma.

For gene expression analysis, RNA was isolated from 59 early-passage samples: 54 OSECs and 5 FTSECs from cell cultures collected at ~80% confluency using the Qiagen miRNAeasy kit with on-column DNase I digestion. RNA (500 ng) was reverse transcribed using the Superscript III kit (Life Technologies). We preamplified 10 ng of cDNA using TaqMan Preamp Mastermix; the resulting product was diluted 1:60 and used to quantify gene expression with the following TaqMan gene expression probes: *WNT4*, Hs01573504_m1; *RSPO1*, Hs00543475_m1; *SYNPO2*, Hs00326493_m1; *ATAD5*, Hs00227495_m1; and *GPX6*, Hs00699698_m1. Four control genes were also included: *ACTB*, Hs00357333_g1; *GAPDH*, Hs02758991_g1; *HMBS*, Hs00609293_g1; and *HPRT1*, Hs02800695_m1 (all Life Technologies). Assays were run on an ABI 7900HT Fast Real-Time PCR system (Life Technologies).

Data analysis. Expression levels for each gene were normalized to the average of all four control genes. Relative expression levels were calculated using the $\Delta\Delta C_t$ method. Genotyping was performed on the iCOGS chips, as described above. Where genotyping data were not available for the most risk-associated SNP, the next most significant SNP was used: rs3820282 at 1p36, rs12023270 at 1p34.3, rs752097 at 4q26, rs445870 at 6p22.1, rs505922 at 9q34.2 and rs3764419 at 17q11.2. Correlations between genotype and gene expression were calculated in R. Genotype-specific gene expression in normal tissue cell lines (eQTL analysis) was compared using the Jonckheere-Terpstra test. Data were normalized to the four control genes, and we tested for eQTL associations, grouping OSECs and FTSECs together. Second, OSECs were analyzed alone. eQTL analyses were performed using three genotype groups or two groups (with the rare homozygote samples grouped together with the heterozygote samples).

eQTL analysis in primary ovarian tumors. eQTL analysis in primary tumors was based on publicly available data from the TCGA Project, which included 489 primary HGSOCs. The methods have been described elsewhere[56]. Briefly, we determined the ancestry for each case on the basis of germline genotype data using EIGENSTRAT software with 415 HapMap genotype profiles as a control set. Only populations of northern and western European ancestry were included. We first performed a *cis*-eQTL analyses using a method we described previously, in which the association between 906,600 germline genotypes and the expression levels of mRNA or miRNA (located within 500 kb on either side of the variant) were evaluated using a linear regression model with the effects of somatic copy number and CpG methylation being deducted. (For miRNA expression, the effect of CpG methylation was not adjusted for because these data were not available.) To correct for multiple tests, we adjusted the test *P* values using the Benjamini-Hochberg method. A significant association was defined by a false discovery rate (FDR) of <0.1.

Having established genome-wide *cis*-eQTL associations in this series of tumors, we then evaluated *cis*-eQTL associations for the top risk associations between each of the six new loci and the gene in closest proximity to the risk SNP. For each risk locus, we retrieved the genotype of all SNPs in ovarian cancer cases on the basis of the Affymetrix 6.0 array. Using these genotypes and the IMPUTE2 March 2012 1000 Genomes Project Phase I integrated variant cosmopolitan reference panel of 1,092 individuals (haplotypes were phased via SHAPEIT), we imputed the genotypes of SNPs in the 1000 Genomes Project in the target regions for TCGA samples[57]. For each risk locus where data for the most risk-associated variant were not available, we retrieved the imputed variants tightly correlated with the most risk-associated variant. We then tested for association between imputed SNPs and gene expression using the linear regression algorithm described above, where each imputed SNP was coded as an expected allele count. Again, significant associations were defined by an FDR of <0.1.

Regulatory profiling of normal ovarian cancer precursor tissues. We performed genome-wide FAIRE and chromatin immunoprecipitation with sequencing (ChIP-seq) for H3K27ac and H3K4me in two normal OSECs, two normal FTSECs and two HGSOC cell lines (UWB1.289 and CAOV3) (S.C., H.S., D.H., K.L. and K.B.K. *et al.*, unpublished data). Cell lines were routinely tested for mycoplasma. These data sets annotate the epigenetic signatures of open chromatin and collectively indicate transcriptional enhancer regions. We analyzed the FAIRE-seq and ChIP-seq data sets and publically available genomic data on promoter and UTR domains, intron-exon boundaries and the positions of noncoding RNA transcripts to identify SNPs from the 100:1 likely causal set that aligned with biofeatures that might provide evidence of SNP functionality.

Candidate gene analysis using genome-wide profiling of primary ovarian cancers. *Data sets: the TCGA Project and COSMIC data sets.* TCGA has performed extensive genomic analysis of tumors from a large number of tissue types, including almost 500 high-grade serous ovarian tumors. These data include somatic mutations, DNA copy number, mRNA and miRNA expression, and DNA methylation. COSMIC is the catalog of somatic mutations in cancer that collates information on mutations in tumors from the published literature[58]. They have also identified the Cancer Gene Census, which is a list of genes known to be involved in cancer. Data are available on a large number of tissue types, including 2,809 epithelial ovarian tumors.

Somatic coding sequence mutations. We analyzed all genes for coding somatic sequence mutations generated from either whole-exome or whole-genome sequencing. In TCGA, whole-exome sequencing data were available for 316 high-grade serous EOC cases. In addition, we determined whether mutations had been reported in COSMIC[58] and whether the gene was a known cancer gene in the Sanger Cancer Gene Census.

mRNA expression in tumor and normal tissue. Normalized and gene expression values (level 3) from gene expression profiling data were obtained from the TCGA data portal for three different platforms (Agilent, Affymetrix HuEx and Affymetrix U133A). We analyzed only the 489 primary serous ovarian tumor samples included in the final clustering analysis[57] and 8 normal fallopian tube samples. The boxplot function in R was used to compare ovarian tumor samples to the fallopian tube samples for 91 coding genes with expression data on any platform within a 1-Mb region around the most significant SNP at the 6 loci. A difference in relative expression between EOC samples and normal tissue was analyzed using the Wilcoxon rank-sum test.

DNA copy number analysis. Serous EOC samples for 481 tumors with $\log_2$ copy number data were analyzed using the cBio Portal for the analysis of TCGA data[59,60]. For each gene in a region, the classes of copy number; homozygous deletion, heterozygous loss, diploid, gain and amplification were queried individually using the advanced onco query language (OQL) option. At a region, the frequency of gain and amplification were combined as 'gain', and homozygous deletion and heterozygous loss were combined as 'loss'.

Analysis of copy number versus mRNA expression. Serous EOC samples for 316 complete tumors (those with CNA, mRNA and sequencing data) were analyzed. Graphs were generated using the cBio Portal for the analysis of TCGA data, and the settings were mRNA expression data *z* score (all genes) with a *z*-score threshold of 2 (default setting) and putative CNAs (GISTIC). The *z* score was the number of s.d. away from the mean of expression in the reference population. GISTIC is an algorithm that attempts to identify significantly altered regions of amplification or deletion across sets of patients.

Luciferase reporter assays. The putative causal SNPs at the 1p36 locus lie in the *WNT4* promoter, and we therefore tested their effect on transcription in a luciferase reporter assay (**Fig. 2d**). Wild-type and risk haplotype (comprising five correlated variants) sequences corresponding to the region bound by hg19 coordinates chr. 1: 22,469,416–22,470,869 were generated by Custom Gene Synthesis (GenScript) and then subcloned into pGL3-basic (Promega). Equimolar amounts of luciferase constructs (800 ng) and pRL-TK *Renilla* (50 ng) were cotransfected into ~8×10^4 iOSE4 (ref. 61) normal ovarian cells in triplicate wells of 24-well plates using Lipofectamine 2000 (Life Technologies). Independent transfections were repeated three times. The Dual-Glo Luciferase Assay kit (Promega) was used to assay luciferase activity 24 h after transfection using a BioTek Synergy H4 plate reader. Statistical significance was tested by log transforming the data and performing two-way ANOVA, followed by Dunnett's multiple-comparisons test in GraphPad Prism. The iOSE4 cell line (derived by K. Lawrenson) was maintained under standard conditions; it was routinely tested for mycoplasma and underwent short tandem repeat profiling.

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Original Investigation

Association of Type and Location of *BRCA1* and *BRCA2* Mutations With Risk of Breast and Ovarian Cancer

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IMPORTANCE Limited information about the relationship between specific mutations in *BRCA1* or *BRCA2* (*BRCA1/2*) and cancer risk exists.

OBJECTIVE To identify mutation-specific cancer risks for carriers of *BRCA1/2*.

DESIGN, SETTING, AND PARTICIPANTS Observational study of women who were ascertained between 1937 and 2011 (median, 1999) and found to carry disease-associated *BRCA1* or *BRCA2* mutations. The international sample comprised 19 581 carriers of *BRCA1* mutations and 11 900 carriers of *BRCA2* mutations from 55 centers in 33 countries on 6 continents. We estimated hazard ratios for breast and ovarian cancer based on mutation type, function, and nucleotide position. We also estimated RHR, the ratio of breast vs ovarian cancer hazard ratios. A value of RHR greater than 1 indicated elevated breast cancer risk; a value of RHR less than 1 indicated elevated ovarian cancer risk.

EXPOSURES Mutations of *BRCA1* or *BRCA2*.

MAIN OUTCOMES AND MEASURES Breast and ovarian cancer risks.

RESULTS Among *BRCA1* mutation carriers, 9052 women (46%) were diagnosed with breast cancer, 2317 (12%) with ovarian cancer, 1041 (5%) with breast and ovarian cancer, and 7171 (37%) without cancer. Among *BRCA2* mutation carriers, 6180 women (52%) were diagnosed with breast cancer, 682 (6%) with ovarian cancer, 272 (2%) with breast and ovarian cancer, and 4766 (40%) without cancer. In *BRCA1*, we identified 3 breast cancer cluster regions (BCCRs) located at c.179 to c.505 (BCCR1; RHR = 1.46; 95% CI, 1.22-1.74; $P = 2 \times 10^{-6}$), c.4328 to c.4945 (BCCR2; RHR = 1.34; 95% CI, 1.01-1.78; $P = .04$), and c. 5261 to c.5563 (BCCR2', RHR = 1.38; 95% CI, 1.22-1.55; $P = 6 \times 10^{-9}$). We also identified an ovarian cancer cluster region (OCCR) from c.1380 to c.4062 (approximately exon 11) with RHR = 0.62 (95% CI, 0.56-0.70; $P = 9 \times 10^{-17}$). In *BRCA2*, we observed multiple BCCRs spanning c.1 to c.596 (BCCR1; RHR = 1.71; 95% CI, 1.06-2.78; $P = .03$), c.772 to c.1806 (BCCR1'; RHR = 1.63; 95% CI, 1.10-2.40; $P = .01$), and c.7394 to c.8904 (BCCR2; RHR = 2.31; 95% CI, 1.69-3.16; $P = .00002$). We also identified 3 OCCRs: the first (OCCR1) spanned c.3249 to c.5681 that was adjacent to c.5946delT (6174delT; RHR = 0.51; 95% CI, 0.44-0.60; $P = 6 \times 10^{-17}$). The second OCCR spanned c.6645 to c.7471 (OCCR2; RHR = 0.57; 95% CI, 0.41-0.80; $P = .001$). Mutations conferring nonsense-mediated decay were associated with differential breast or ovarian cancer risks and an earlier age of breast cancer diagnosis for both *BRCA1* and *BRCA2* mutation carriers.

CONCLUSIONS AND RELEVANCE Breast and ovarian cancer risks varied by type and location of *BRCA1/2* mutations. With appropriate validation, these data may have implications for risk assessment and cancer prevention decision making for carriers of *BRCA1* and *BRCA2* mutations.

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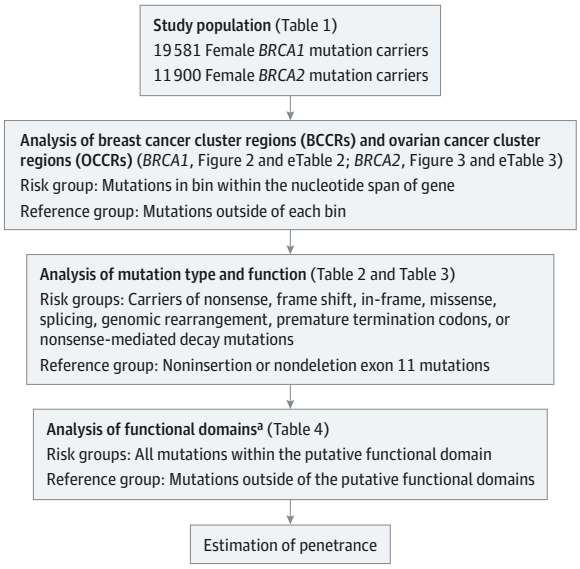
Women who have inherited mutations in *BRCA1* (17q21, chromosome 17: base pairs 43,044,294 to 43,125,482) or *BRCA2* (13q12.3, chromosome 13: base pairs 32,315,479 to 32,399,671) have an increased risk of breast and ovarian cancers.[1,2] Little is known about how cancer risks differ by *BRCA1* or *BRCA2* (*BRCA1/2*) mutation type. An "ovarian cancer cluster region" (OCCR) has been reported in both *BRCA1* and *BRCA2* using small sample sets. For *BRCA1*, initially mutations after exon 11 were associated with a 20% lower ovarian cancer risk than mutations in exons 1 through 11.[3] Following that observation, Thompson et al[4] reported an increased risk of ovarian vs breast cancer specifically was associated with mutations in the central portion of exon 11. This association was attributed to both a decrease in breast cancer risk and an increase in ovarian cancer risk in this region. Mutations in exon 11 of *BRCA2* also have been associated with higher ovarian vs breast cancer risk than in other regions of the gene.[5] It was hypothesized that this risk variation might be explained by the failure of *BRCA1/2* exon 11 truncating mutations to trigger nonsense-mediated messenger RNA (mRNA) decay (NMD) because of their extremely large size, contrary to truncating mutations in smaller exons. However, this postulate was not supported by the measures of the relative amounts of mRNA transcript encoded by *BRCA1/2* alleles.[6,7] Murine models of different mutations in *BRCA1/2* also suggest that genotype-phenotype correlations exist.[8,9] To our knowledge, no study has reported whether *BRCA1/2* mutation type is associated with differences in breast and ovarian cancer risk. Thus, we evaluated whether *BRCA1* and *BRCA2* mutation type or location is associated with variation in breast and ovarian cancer risk.

Methods

The Consortium of Investigators of Modifiers of BRCA (CIMBA) initiative is an international collaboration of centers on 6 continents that has collected information about carriers of disease-associated *BRCA1* and *BRCA2* mutations with associated clinical, risk factor, and genetic data.[10] All carriers participated in clinical assessment or research studies at the host institutions after providing informed consent under protocols approved by institutional review boards. For some individuals, ascertainment date reflects the earliest date at which they came to the attention of a clinician or research investigator (eg, when they were first seen in a clinic), even though their research participation, genetic testing, and research data collection may have occurred many years later. Fifty-five centers and multicenter consortia (eTable 1 in the Supplement) in 33 countries submitted deidentified data that met the CIMBA inclusion criteria.[10] Study eligibility criteria included carriage of a disease-associated mutation and clinical data necessary to estimate hazard ratios (ie, cancer diagnosis, ascertainment and follow-up dates). Women were excluded if they carried both a *BRCA1* and *BRCA2* mutation (n = 84).

No races/ethnicities were excluded from this study. All races/ethnicities were included in this report to provide maximal generalizability of results for populations who may be undergoing genetic testing and counseling. All race/ethnicity designations were based on self-report. Race/ethnicity data were collected across the various centers using either fixed categories or open-ended questions.

Figure 1. Analysis Workflow



Analyses undertaken are listed in the order in which they are presented in the text.

[a] The functional domains were the RING, coiled coil, BRCT, BRC, DNA binding, oligonucleotide-binding folds, and tower domains.

Mutation Classification

Only carriers with clearly pathogenic *BRCA1/2* mutations were included in this analysis. Pathogenic mutations were defined as (1) mutations generating a premature termination codon, except variants generating a premature termination codon in exon 27 after codon 3010 of *BRCA2*[11]; (2) large in-frame deletions that span 1 or more exons; and (3) deletions of transcription regulatory regions (promoter and/or first exon) expected to cause lack of expression of mutant allele. We also included missense variants considered pathogenic by the Breast Cancer Information Core committee or published variants classified as pathogenic using multifactorial likelihood approaches.[12,13]

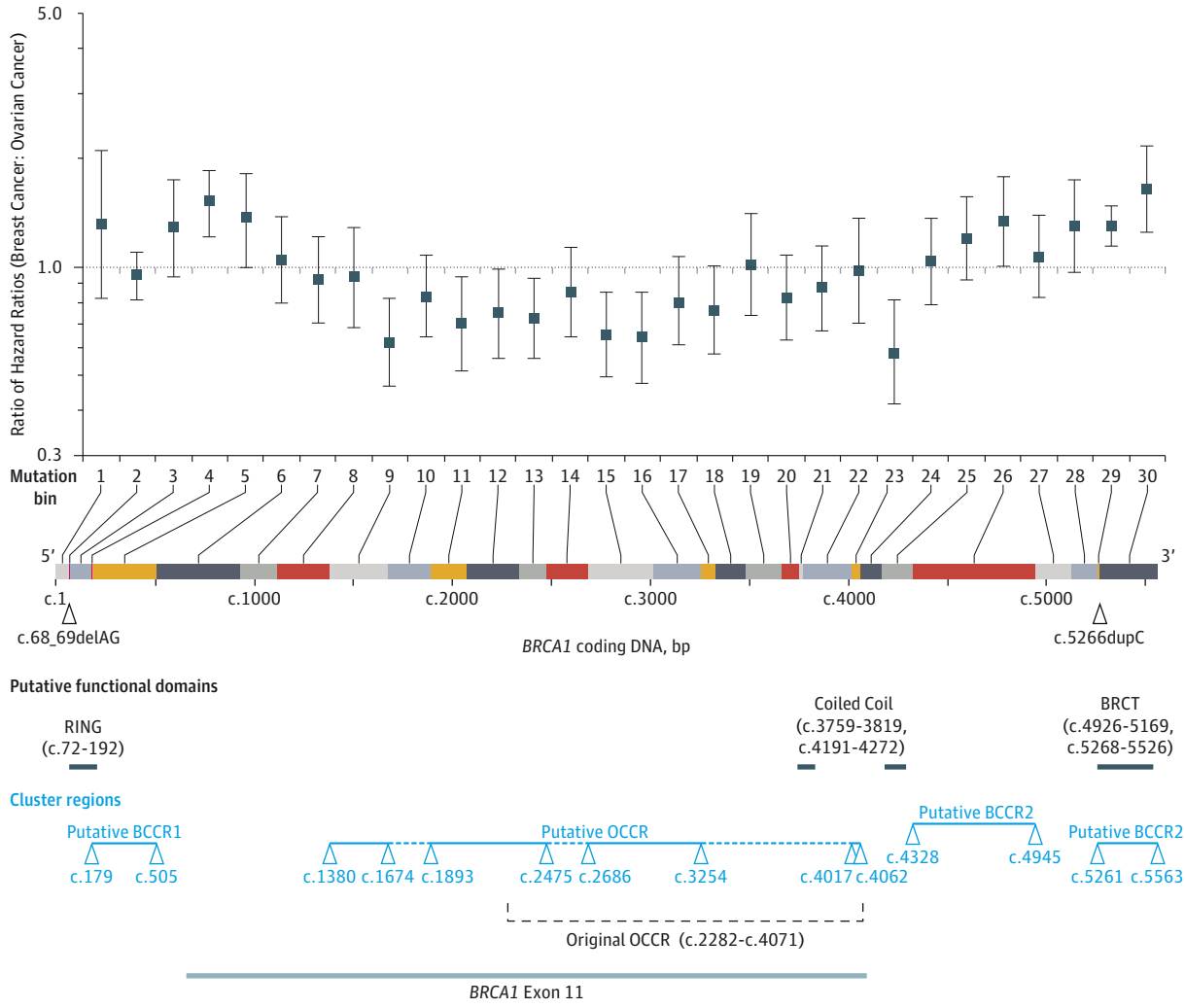
Mutations are described here using the Human Genome Variation Society nomenclature in which the nucleotide numbering is from the A of the ATG translation initiator codon, and use the c.XXX numbering convention (eAppendix 1 in the Supplement).

Creation of Mutation Groups for Analysis

Mutation Bins

To identify segments across the intronic and exonic regions of the *BRCA1* or *BRCA2* genes associated with different breast vs ovarian cancer risks, we created bins of mutations by base pair location (**Figure 1**). We divided the genomic regions of both genes to create bins of genomic sequence that contained

Figure 2. Hazard Ratio of Breast Cancer Relative to the Hazard Ratio of Ovarian Cancer by *BRCA1* Nucleotide Position



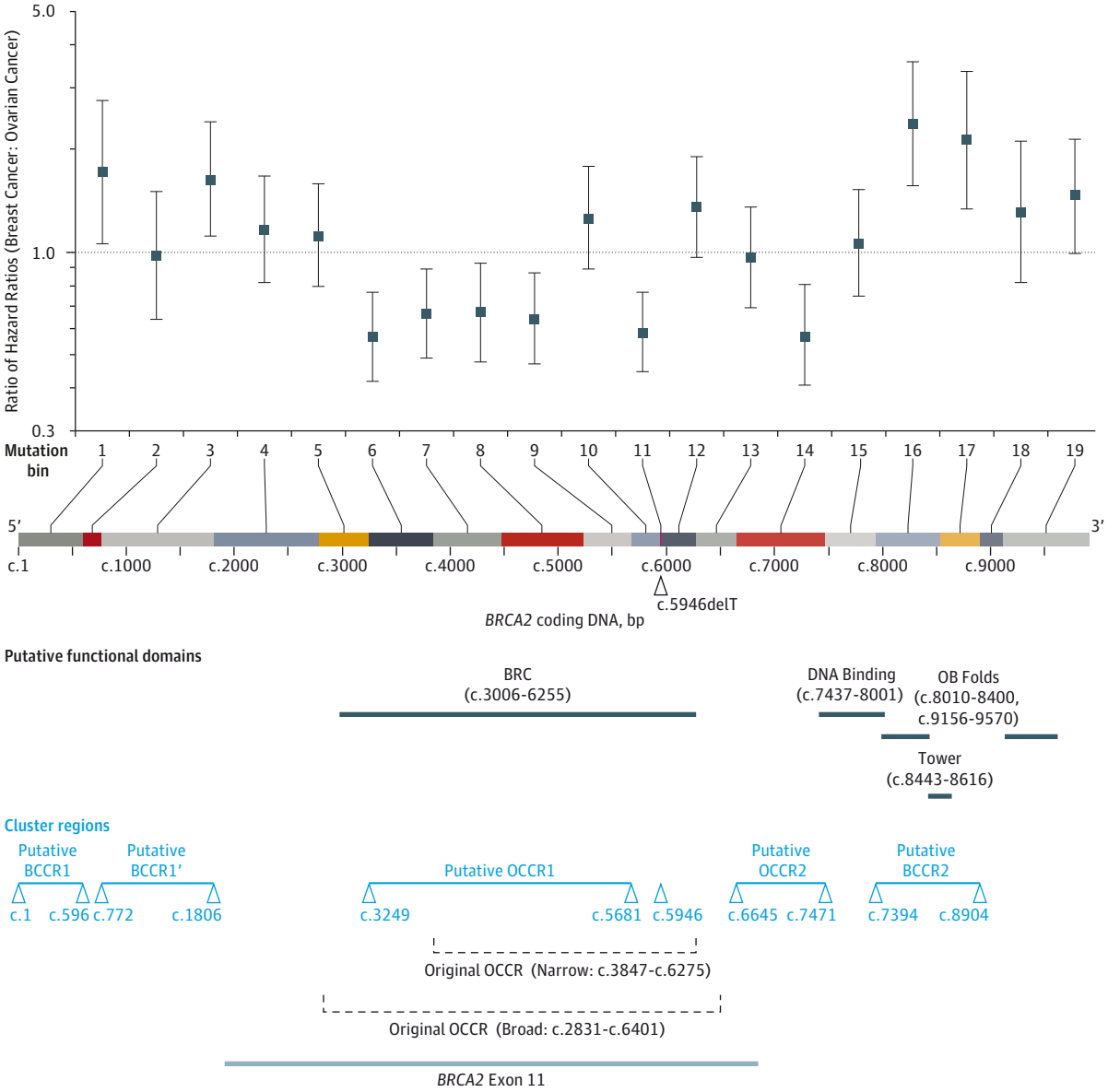
The graph shows the ratio of hazard ratios (blue data markers) and 95% CI (error bars) for the mutation bins defined across the span of the coding DNA sequence of the *BRCA1* gene. Black arrowheads under the bins indicate 2 founder mutations of clinical interest in the Ashkenazi Jewish population. Regions inferred to be breast cancer cluster regions (BCCRs) and ovarian cancer cluster regions (OCCRs) are shown at the bottom. Solid light blue lines indicate regions found to be statistically significant; dashed light blue lines indicate regions in the same direction of effect that were not statistically significant. eTable 2 in the Supplement lists the bins and risks used to define the BCCRs and OCCRs.

all deleterious mutations regardless of category or function. Bins were constructed by using an algorithm in which each bin contained approximately equal numbers of participants with bin length defined by distance in base pairs. We excluded large genomic rearrangements from this analysis as those mutations span multiple bins and also undertook a subset analysis with and without missense mutations. The resulting bins are presented in **Figure 2** and eTable 2 in the Supplement for *BRCA1* and **Figure 3** and eTable 3 in the Supplement for *BRCA2*.

Mutation Type and Functional Domains

Mutations were grouped by type and function as frame shift, nonsense, missense, splice site, and then by in-frame and out-of-frame. Mutation groups included individuals who carried in-frame deletions, nonsplice out-of-frame deletions, and out-of-frame deletions. Missense mutations in *BRCA1* were grouped into those within the RING[14,15] and BRCT domains.[16-19] Only 17 *BRCA2* carriers (0.1%) had missense mutations classified as pathogenic; these were removed from the analysis because the sample size was too small to provide statistically meaningful inferences. Comparisons also were made of mutations predicted not to lead to NMD vs those that do lead to NMD. Mutations predicted not to cause NMD were defined as those that lead to a stop codon within 50 nucleotides before or within the last exon.[20] In *BRCA1*, a subgroup including premature termination codons before c.297, presumed to allow reinitiation of translation at the AUG at that site, was examined separately.[21] Premature termination codons refer to all mutations leading

Figure 3. Hazard Ratio of Breast Cancer Relative to the Hazard Ratio of Ovarian Cancer by *BRCA2* Nucleotide Position



The graph shows the ratio of hazard ratios (blue data markers) and 95% CI (error bars) for the mutation bins defined across the span of the coding DNA sequence of the *BRCA2* gene. The black arrowhead under the bins indicates a founder mutation of clinical interest in the Ashkenazi Jewish population. The regions inferred to be breast cancer cluster regions (BCCRs) and ovarian cancer cluster regions (OCCRs) are shown at the bottom; the solid light blue lines indicate regions found to be statistically significant. eTable 3 in the Supplement lists the bins and risks used to define to define the BCCRs and OCCRs.

to a truncated open reading frame. Putative functional domains in *BRCA1* and *BRCA2* were defined using the boundaries in the Pfam database.[22] We also identified reported domains in *BRCA1* or *BRCA2* that are involved in binding putative proteins.

Statistical Analysis

The primary outcomes of interest were diagnosis of ovarian cancer or breast cancer. For ovarian cancer, observations were censored at the earliest of the following outcomes: bilateral risk-reducing salpingo-oophorectomy, death, or having reached the end of follow-up without an ovarian cancer or other censoring event. In women with both breast and ovarian cancer diagnoses, prior breast cancer diagnoses were ignored in the analysis of ovarian cancer. Time to event was computed from birth to age at first ovarian cancer diagnosis or age at censoring. For the primary event of breast cancer, observations were censored at the earliest of the following outcomes: ovarian cancer, risk-reducing salpingo-oophorectomy, risk-reducing mastectomy, death, or having reached the end of follow-up without a cancer or other censoring event. Time to event was computed from birth to age at first cancer diagnosis or age at

censoring. To account for intracluster dependence due to multiple individuals from the same family, a robust sandwich variance estimate was specified in Cox proportional hazards models.[23] All analyses were undertaken in *BRCA1* and *BRCA2* mutation carriers separately. The proportional hazards assumption was tested using log(−log) plots and Schoenfeld residuals.

Our analyses assessed the relationship of mutation groups with cancer risk. First, we used mutation bins to evaluate whether there is evidence to support the previous report of an OCCR[3,5] and whether breast cancer cluster regions (BCCRs) may exist. To assess whether specific genomic regions of these genes were associated with greater breast vs ovarian cancer risk, we computed the hazard ratio of breast cancer, the hazard ratio of ovarian cancer, and a statistic RHR, defined as the ratio of breast vs ovarian cancer hazard ratio estimates. Values of RHR greater than 1 indicate elevated breast cancer risk; values of RHR less than 1 indicate elevated ovarian cancer risk. We evaluated bins of mutations across the span of *BRCA1* or *BRCA2* compared with all other mutations not contained in that bin by fitting a multiple correlated outcomes model stratified by cancer site.[24] This approach allowed us to achieve 2 goals: first, to estimate the correlation between ovarian and breast cancer outcomes within an individual, and second, to provide an estimate of the RHR (estimated via an interaction term between cancer site and mutation bin) with the correct confidence interval using robust sandwich variance estimates to account for the correlation between outcomes within a woman. All analyses were adjusted for birth year and race, stratified by center, and controlled for clustering within family.

Second, we compared each mutation type or functional group against a common reference group. The use of a common reference group allowed us to compare hazard ratio estimates across different mutation classes. For both *BRCA1* and *BRCA2*, we chose exon 11 nonsense mutations as the common reference group. Exon 11 nonsense mutations are common in diverse ethnic backgrounds and have been demonstrated to have the same biological effect, leading to NMD.[25]

Approximate cancer risks to age 70 years for specific mutation classes were derived from the relative risk estimates. For *BRCA1* and *BRCA2*, estimated lifetime breast cancer penetrances were assumed to be 59% and 51% and ovarian cancer penetrance 34% and 11%, respectively.[26] Mutation-specific penetrance estimates were derived using the method presented in eAppendix 2 in the Supplement.

Statistical tests were judged significant based on 2-sided hypothesis tests with $P < .05$. All P values were corrected for multiple hypothesis testing within each table of results by controlling the false discovery rate (FDR) using the method of Benjamini and Hochberg.[27] Analyses were conducted in SAS version 9 (SAS Institute) or R version 2.7.2 (R Foundation for Statistical Computing).

Results

A total of 19 581 female carriers of *BRCA1* mutations and 11 900 carriers of *BRCA2* mutations were eligible for inclusion in this study. **Table 1** reports the distribution of dates of ascertainment to the study as well as time from ascertainment to cancer diagnosis or censoring, as used in the survival analysis models reported in this section. Mean age of breast cancer diagnosis was 39.9 years in *BRCA1* mutation carriers and 42.8 years in *BRCA2* mutation carriers. Mean age of ovarian cancer diagnosis was 50.0 years in *BRCA1* mutation carriers and 54.5 years in *BRCA2* mutation carriers. The 3 ovarian cancer cases diagnosed before age 18 years were germ cell tumors and included in the analysis (Table 1). Of note, all analyses also were undertaken excluding these 3 cases and there was no difference in the results. The majority of the sample consisted of white women for both *BRCA1* and *BRCA2* mutation carriers: 92% to 93% white, including 8% to 9% Jewish women. Both *BRCA1* and *BRCA2* mutation carriers had a median parity of 2.0 live births and age at menarche of 13 years. Median age at menopause was 44 years in *BRCA1* and 46 years in *BRCA2* mutation carriers, reflecting in part the use of preventive surgeries.

BRCA1: Breast and Ovarian Cancer Cluster Regions

We observed an OCCR bounded by c.1380 and c.4062 (Figure 2), suggesting a relative decrease in breast relative to ovarian cancer risk (RHR = 0.62; 95% CI, 0.56-0.70; FDR-corrected $P = 9 \times 10^{-17}$). This estimate was obtained by considering all mutations across multiple bins spanning the OCCR. The OCCR is explained by both a relative decrease in breast cancer risk and a relative increase in ovarian cancer risk (eTable 2 in the Supplement), which was statistically significant in bins 9, 11-13, 15-16, and 23 (Figure 2). The OCCR extends further 5′ of the previously reported OCCR, which was defined by the interval c.2282 to c.4071.[3] The OCCR is entirely contained within exon 11 (c.670-c.4096) with bins 6 and 23 being approximately coincident with the boundaries of the exon.

We also observed a relative increase in breast cancer risk and a relative decrease in ovarian cancer risk for mutations occurring in the 5′ and 3′ regions of *BRCA1*, potentially defining 2 BCCRs (Figure 2). BCCR1 mutations within bins 4-5 (c.179-c.505) were associated with excess risks of breast vs ovarian cancer (eTable 2 in the Supplement) and lie within the 3′ region of the RING domain (c.72-c.192). Mutations in the BCCR1 were associated with a relative increase in breast cancer risk relative to ovarian cancer risk (RHR = 1.46; 95% CI, 1.22-1.74; FDR-corrected $P = 2 \times 10^{-6}$). When all mutations in the RING domain were considered together as compared with all others, they were associated with a significant increase in breast cancer risk (HR = 1.13; 95% CI, 1.02-1.26) and a significant decrease in ovarian cancer risk (HR = 0.81; 95% CI, 0.67-0.97). Bin 2, which contains only the founder mutation *BRCA1* c.68_69delAG (185delAG), did not provide statistically significant evidence for elevated breast vs ovarian cancer risks, suggesting that this mutation is associated with relatively equivalent risks of both cancers.

Mutations in bins 26 and 29-30 in the 3′ region of *BRCA1* also provided evidence for additional BCCRs. BCCR2 was associated with an increase in breast cancer relative to ovarian cancer risk (RHR = 1.34; 95% CI, 1.01-1.78; $P = .04$) bounded by c.4328 and c.4945. The second segment of this BCCR (denoted BCCR2′) includes the BRCT domains (c.4926-c.5169 and

Table 1. Characteristics of Study Sample: Ascertainment, Diagnosis, Demographics, and Risk Factors

	BRCA1 Mutation Carriers			*BRCA2* Mutation Carriers		
Variable	No.	Median or Mean (Range)	SD	No.	Median or Mean (Range)	SD
Women with breast cancer	10 093			6452		
Year of breast cancer diagnosis		1999 (1942-2011)			1999 (1937-2011)	
Mean age at breast cancer diagnosis, y		39.9 (17-85)	9.2		42.8 (17-86)	9.8
Women without breast cancer	9488			5448		
Mean age of women with no breast cancer diagnosis, y		41.0 (12-102)[a]	12.0		42.6 (13-94)[a]	13.1
Women with ovarian cancer	3358			954		
Year of ovarian cancer diagnosis		2001 (1949-2011)			2001 (1967-2010)	
Mean age at ovarian cancer diagnosis, y		50.0 (16-92)[b]	9.5		56.5 (19-89)[b]	9.9
Women without ovarian cancer	16 223			10 946		
Mean age of women with no ovarian cancer diagnosis, y		42.0 (12-102)[a]	12.0		45.4 (13-96)[a]	12.6
Race/ethnicity						
White	16 481			10 014		
African/African American	176			87		
Asian	392			404		
Hispanic	333			175		
Jewish	1800			971		
Other	399			249		
Parity, No. of live births		2.0 (0-14)	1.4		2.0 (0-14)	1.4
Age at menarche, y		13.0 (8-23)	1.5		13.0 (7-22)	1.6
Age at natural or surgical menopause, y		44.0 (16-68)	6.3		46.0 (14-68)	6.6

[a] Includes age at time of original family ascertainment for some women who were never diagnosed with cancer.

[b] Includes 3 germ cell carcinoma cases diagnosed before age 21 years.

c.5268-c.5526) and was associated with a relative excess of breast vs ovarian cancers (RHR = 1.38; 95% CI, 1.22-1.55; $P = 6 \times 10^{-9}$) (Figure 2). In the BRCT domains, the preponderance of mutations was missense, not expected to trigger NMD. This region also includes bin 29, which contains only the *BRCA1* c.5266dupC (5382insC) mutation, which also is not predicted to lead to NMD as it introduces a premature termination codon in the last exon.[6] In bin 30, *BRCA1* c.5277 + 1G>A, a common splice site mutation in the Netherlands, is observed and not expected to lead to NMD.

We compared breast and ovarian cancer risks between women who had a mutation in a specified functional domain compared with all other women who did not have mutations in that domain. Mutations in the RING domain were associated with higher breast cancer risks and nonsignificant lower ovarian cancer risks than other mutations. These results are consistent with the colocation of the BCCR1 (Figure 2) and RING domain. Mutations in the BRCT domains were associated with higher breast cancer risk. When analyses were limited to mutations conferring NMD, breast cancer risk became significantly associated with mutations in the coiled coil domain.

BRCA1: Risks by Category and Function

We observed variability in breast and ovarian cancer risks by mutation class (**Table 2** and **Table 3**). For *BRCA1*-associated breast cancer, most risk groups were associated with higher breast cancer risk than the exon 11 nonsense mutation reference group. This result is consistent with the data shown in Figure 2 and eTable 2 in the Supplement as it is similar in location with the OCCR. Groups with elevated breast cancer risk include all mutations leading to NMD (group 1), all premature termination codon mutations except for exon 11 nonsense mutations (group 2), frame shift and nonsense mutations occurring 5′ of c.297 that are predicted to lead to NMD and reinitiation (group 3), nonpremature termination codon mutations (group 4), all founder mutations (group 5) and the founder mutation c.5266dup C (group 5b), missense mutations (group 6) and missense mutations in the RING domain (group 6a), missense and in-frame deletions (group 7), all in-frame deletions (group 8), and premature termination codon mutations not leading to NMD (group 9). The majority of the last group is comprised of c.5266dupC (83%). For *BRCA1*-associated ovarian cancer (Table 2), mutations associated with significantly lower ovarian cancer risks compared with the reference group included mutations 5′ of c.297 (group 3), nonpremature termination codons (group 4), founder mutations (group 5, 5a, 5b), missense mutations (group 6, 6a), missense and in-frame deletions (group 7), and premature termination codons not leading to NMD (group 9).

When comparing mean age differences among women with or without a specific mutation category or function, we found small but statistically significant differences. In *BRCA1,* exon 11 mutations were associated with earlier ages at breast and ovarian cancer diagnosis. Mutations conferring NMD or premature termination codon were associated with a later age at breast cancer diagnosis. Conversely, an earlier

Table 2. Mutation-Specific Risk Groups: Risks Relative to Noninsertion or Nondeletion Exon 11 Mutations

Group	Description	Mutation Types Included	NMD	Protein	No. (%) With Mutation	Breast Cancer, HR (95% CI)	No. of Women With Breast Cancer	Ovarian Cancer, HR (95% CI)	No. of Women With Ovarian Cancer
BRCA1 **(n = 19 581)**									
a	Exon 11 nonsense mutations	NS	Yes	No	1770 (9.0)	1 [Reference]	796	1 [Reference]	336
1	NMD	FS, NS, OF-GR, OF-SP	Yes	No	11 027 (56.3)	1.20 (1.08-1.33)	5469	0.94 (0.80-1.11)	2038
2	All premature termination mutations	FS, NS, OF-GR, OF-SP	Yes	No	14 453 (73.8)	1.25 (1.12-1.38)	7318	0.93 (0.79-1.09)	2524
3	Mutations before c.297 ATG presumed transcription reinitiation	FS, NS	No	No	2763 (14.1)	1.40 (1.12-1.74)	250	0.66 (0.46-0.95)	74
4	Not premature termination	MS, IF, GR, IF-SP, FS	No	Yes	5398 (27.6)	1.51 (1.34-1.70)	2986	0.73 (0.61-0.88)	781
5	All founder mutations	FS			5375 (27.5)	1.41 (1.23-1.61)	2698	0.72 (0.60-0.88)	850
5a	Founder mutation c.68_69delAG	FS		No	2324 (11.9)	1.14 (0.94-1.38)	1033	0.67 (0.51-0.87)	391
5b	Founder mutation c.5266dupC	FS		Yes	3051 (15.6)	1.63 (1.41-1.89)	1665	0.73 (0.57-0.92)	459
6	All missense mutations	MS		Yes	1620 (8.3)	1.40 (1.20-1.64)	899	0.73 (0.57-0.92)	241
6a	Missense mutations in RING domain (c.72-192)	MS		Yes	1213 (6.2)	1.56 (1.32-1.84)	681	0.73 (0.56-0.96)	171
6b	Missense mutations in BRCT domain (c.4866-5325)	MS		Yes	372 (1.9)	1.09 (0.82-1.45)	202	0.72 (0.48-1.09)	64
7	Missense mutations and in-frame deletions	MS+IF, IF-SP, IF-GR		Yes	1658 (8.5)	1.42 (1.22-1.66)	925	0.71 (0.56-0.91)	249
8	In-frame deletions (splice, single codon, large deletion)	IF, IF-SP, IF-GR		Yes	38 (0.2)	2.41 (1.41-4.11)	26	0.51 (0.15-1.76)	8
9	All premature termination codons not leading to NMD	FS, NS, OF-SP, OF-GR	No	Yes	3663 (18.7)	1.58 (1.38-1.80)	2000	0.74 (0.60-0.91)	520
BRCA2 **(n = 11 900)**									
a	Exon 11 nonsense mutations	NS	Yes	No	1001 (8.4)	1 [Reference]	534	1 [Reference]	155
1	NMD	FS, NS, OF-GR, OF-SP	Yes	No	9961 (83.7)	1.10 (0.95-1.27)	5383	0.78 (0.56-1.08)	803
2	Not premature termination codon	IF-S, IF-FS, NS	No	Yes	203 (1.7)	1.35 (0.92-1.97)	118	0.34 (0.13-0.88)	12
3	In-frame deletions (splice, frame shift)	IF-FS, IF-S	No	Yes	117 (1.0)	1.41 (0.85-2.35)	76	0.26 (0.08-0.88)	9
4	Premature termination codons in last exon not leading to NMD	FS, NS	No	Yes	86 (0.7)	1.32 (0.79-2.19)	42	0.51 (0.13-2.09)	3
5	Founder mutation c.5946delT				1341 (11.3)	0.79 (0.60-1.03)	579	0.77 (0.46-1.32)	155

Abbreviations: FS, frame shift; GR, genomic rearrangement; HR, hazard ratio; IF, in-frame; NE, not estimable; NMD, nonsense-mediated decay; NS, nonsense; MS, missense; OF, out of frame; SP, splicing.

age at breast cancer diagnosis was associated with nonpremature termination codon mutations and the founder mutations (Table 3).

BRCA2: Breast and Ovarian Cancer Cluster Regions

We observed an OCCR (OCCR1) bounded by c.3249 and c.5681, containing c.5946delT (6174delT), with statistically significant evidence for a relatively higher ovarian cancer vs breast cancer risk among carriers of mutations in bins 6-9 and 11 (Figure 3). OCCR1 is explained by both a relative increase in ovarian cancer risk and a relative decrease in breast cancer risk, with an increase in ovarian cancer relative to breast cancer risk (RHR = 0.51; 95% CI, 0.44-0.60; $P = 6 \times 10^{-17}$) (eTable 3 in the Supplement). The putative OCCR1 lies within the previously reported OCCR[3] and approximately colocalized with the BRC repeats within exon 11.[17,18,28] A second putative OCCR (OCCR2) outside of the original OCCR boundaries also was observed defined by bin

Table 3. Mutation-Specific Risk Groups: Ages at Diagnosis of Breast Cancer or Ovarian Cancer

Group[a]	No. of Women With Breast Cancer	No. of Women With Ovarian Cancer	Mean Age at Diagnosis, y					
			Breast Cancer			Ovarian Cancer		
			With Mutation	Without Mutation	FDR *P* Value	With Mutation	Without Mutation	FDR *P* Value
BRCA1 **(n = 19 581)**								
a	796	336	40.4	42.4	<.001	50.2	52.5	<.001
1	5469	2038	41.2	40.1	<.001	50.8	50.3	.32
2	7318	2524	41.2	40.4	.001	51.2	50.2	.06
3	250	74	40.7	39.4	.07	50.5	52.2	.29
4	2986	781	40.5	41.1	.006	50.6	50.0	.32
5	2698	850	40.2	41.1	<.001	50.27	51.11	.03
5a	1033	391	40.43	42.41	<.001	50.22	52.49	<.001
5b	1665	459	40.5	41.5	<.001	50.6	50.0	.34
6	899	241	40.6	49.8	.60	50.5	49.8	.59
6a	681	171	40.6	41.1	.39	50.6	49.3	.32
6b	202	64	40.7	40.2	.60	50.5	51.2	.59
7	925	249	40.6	40.9	.60	50.6	49.8	.34
8	26	8	40.6	41.8	.60	50.5	48.4	.59
9	2000	520	40.5	41.1	.02	50.6	50.1	.34
BRCA2 **(n = 11 900)**								
a	534	155	43.3	45.8	<.001	56.5	56.9	.83
1	5383	803	44.5	43.4	.008	56.5	56.5	.93
2	118	12	42.4	43.6	.42	55.7	55.6	.94
3	76	9	42.4	43.6	.42	56.3	56.5	.94
4	42	3	42.4	43.6	.50	53.0	56.5	.94
5	579	155	43.33	45.83	<.001	56.47	56.88	.65

Abbreviations: FDR, false discovery rate.

[a] Group descriptions appear in Table 2.

14 (c.6645-c.7471). OCCR2 was associated with an increase in ovarian cancer relative to breast cancer risk (RHR = 0.57; 95% CI, 0.41-0.80; *P* = .001).

We also observed a relative increase in breast cancer risk and a relative decrease in ovarian cancer risk for mutations occurring in the 5′ and 3′ regions of *BRCA2*, potentially defining multiple BCCRs (ie, BCCR1, BCCR1′, and BCCR2) (Figure 3). These 3 regions were associated with relatively increased breast cancer risk relative to ovarian cancer risk with RHR = 1.71 (95% CI, 1.06-2.78; *P* = .03), RHR = 1.63 (95% CI, 1.10-2.40; *P* = .01), and RHR = 2.31 (95% CI, 1.69-3.16; *P* = .00002), respectively. These regions were associated with both increased breast cancer risk and decreased ovarian cancer risk (eTable 3 in the Supplement).

We also observed small but statistically significant differences in the mean age at breast cancer diagnosis associated with some of these regions. The mean age was greater for mutations in OCCR vs mutations not in OCCR (45.0 vs 43.9 years, *P* < .001; mean difference: 1.17; 95% CI, 0.65 to 1.69), lower for mutations in BCCR1 vs mutations not in BCCR1 (42.6 vs 44.3 years; *P* = .004; mean difference: −1.66, 95% CI, −2.80 to −0.53), and lower for mutations in BCCR2 vs mutations not in BCCR2 (43.5 vs 44.3 years, *P* = .04; mean difference: −0.80, 95% CI, −1.55 to −0.05).

To complement the prior set of analyses, we also present associations of breast and ovarian cancers among groups of *BRCA2* mutation carriers defined by known DNA binding domains (**Table 4**). Mutations in the BRC repeats were associated with lower breast cancer risks and higher ovarian cancer risks than those mutations not occurring in the BRC repeats consistent with their colocation with the OCCR1 (Figure 3).

BRCA2: Risks by Category and Function

For *BRCA2*-associated cancer, the reference exon 11 mutation group was associated with decreased breast cancer risk compared with most other mutation classes (Table 2), consistent with colocalization with OCCR1. Compared with the reference group, ovarian cancer risks were further reduced among women who carried premature truncation codons (HR = 0.27; 95% CI, 0.11-0.66). We observed an association with earlier age at breast cancer diagnosis with exon 11 mutations and for mutations not conferring NMD (Table 3).

Absolute Risks

To illustrate potential mutation-specific effects on absolute cancer risks, we used the hazard ratio estimates to derive approximate absolute risks and 95% confidence intervals, based on published estimates for the overall risks of breast and ovarian cancer by age 70 years.[26] These estimates are for illustration and do not represent absolute risk estimates that would be required in a genetic counseling setting, as

Table 4. Risks Associated With Specific Binding Domains: Comparison of Mutations Not in the Domain (ie, the Reference Group) vs Those Within the Domain

				Breast Cancer			Ovarian Cancer		
Gene	Domain	Binding Partner	Region	No. With/Without Mutation[a]	HR (95% CI)	FDR *P* Value	No. With/Without Mutation[a]	HR (95% CI)	FDR *P* Value
BRCA1	RING	BARD1	c.72-192	781/595	1.13 (1.02-1.26)[b,c]	.04	205/1171	0.81 (0.67-0.97)	.07
	Coiled coil	PALB2	c.3759-3819 or c.4191-4272	122/90	1.20 (0.93-1.54)[d]	.16	39/173	0.97 (0.62-1.50)	.88
	BRCT	BACH1	c.4926-5169 or c.5268-5526	1203/832	1.26 (1.15-1.38)[e,f]	<.001	298/1737	0.86 (0.74-1.01)	.09
BRCA2	BRC	RAD51	c.3006-3108, c.3636-3738, c.4263-4365, c.4551-4653, c.4992-5094, c.5511-5613, c.5913-6015, or c.6153-6255	810/992	0.67 (0.56-0.79)[g,h]	<.001	205/1597	1.09 (0.78-1.53)	.77
	DNA binding		c.7437-8001	464/336	1.17 (0.99-1.38)	.08	63/737	1.06 (0.71-1.59)	.77
	OB folds	ssDNA	c.8010-8400 or c.9156-9570	512/364	1.18 (1.01-1.37)[h,i]	.07	50/826	0.57 (0.39-0.84)	.02
	Tower	RAD51	c.8443-8616	193/154	1.20 (0.92-1.56)	.19	18/329	0.42 (0.18-1.00)[j]	.10

Abbreviations: FDR, false discovery rate; HR, hazard ratio; NMD, nonsense-mediated decay; OB, oligonucleotide-binding.

[a] Among 19 581 carriers of *BRCA1* mutations and 11 900 carriers of *BRCA2* mutations.

[b] Missense mutations only: HR = 1.42; 95% CI, 1.06-1.90.

[c] Mutations conferring NMD only: HR = 2.56; 95% CI, 1.03-6.34.

[d] Mutations conferring NMD only: HR = 1.35; 95% CI, 1.05-1.72.

[e] Premature termination codon mutations only: HR = 1.31; 95% CI, 1.17-1.47.

[f] Mutations conferring NMD only: HR = 1.38; 95% CI, 1.20-1.59.

[g] Premature termination codon mutations only contributed to this estimate.

[h] Mutations conferring NMD only: HR = 1.26; 95% CI, 1.07-1.48.

[i] Premature termination codon mutations only: HR = 1.26; 95% CI, 1.07-1.48.

[j] Mutations conferring NMD only: HR = 0.31; 95% CI, 0.13-0.77.

Table 5. Representative Cancer Penetrances by Age 70 Years: Baseline Risk and Modified Risk in Mutation Group

Gene	Cancer Site	Statistically Significant Mutation-Specific Relative Risk	Mutation Groups Corresponding to These Relative Risks, Tables 2-3 (Group No.)	Mutation Prevalence, %[a] (EMBRACE Data)	Overall Penetrance to Age 70 Years, % (BOADICEA)	Mutation-Specific Penetrance to Age 70 Years, % (95% CI)
BRCA1	Breast	1.4	All founder mutations (5)	16	59	69 (56-83)
	Ovary	0.7	All founder mutations (5)	16	34	26 (10-43)
BRCA2	Breast	0.7	Truncating mutations within the BRC domains (Table 3)	11	51	40 (27-54)
	Ovary	0.3	Not PTC (2)	0.6	11	3 (0-38)

[a] Defined as the proportion of heterozygous mutation carriers with this mutation class with the specified cancer and *BRCA1* or *BRCA2* mutation in the EMBRACE data set.

they do not account for noncancer outcomes that may influence a woman's life expectancy, the effects of family history, and nonrandom ascertainment of mutation carriers in this sample and depend on assumptions about the prevalence of different mutation classes in the population. Using the *BRCA1/2* baseline breast and ovarian cancer risks of Antoniou et al,[26] we estimated risks and confidence intervals about these risks (eAppendix 2 in the Supplement). These confidence limits assume that the overall risk for a given individual is provided by our estimates and should not be interpreted as measuring the overall uncertainty in the absolute risk estimates, as shown in **Table 5**. The overall breast cancer risk for *BRCA1* mutation carriers by age 70 years is 59%, which increases to 69% (95% CI, 56%-83%) in women who carry a missense mutation, Jewish founder mutation, or a mutation that undergoes NMD with reinitiation. The ovarian cancer risk in *BRCA1* mutation carriers by age 70 years is 34% overall but decreases to 26% (95% CI, 10%-43%) among women who carry a founder mutation.

Discussion

We have identified mutations in *BRCA1* or *BRCA2* that are associated with significantly different risks of breast and ovarian cancers. These mutation-specific risks coincide with known or hypothesized functional domains and provide a basis around which accurate risk estimates can be generated for women who have inherited a particular *BRCA1/2* mutation. These results are consistent with prior reports of OCCRs in both *BRCA1* and *BRCA2* that lie in or near exon 11 of both genes.[3,5,29,30] Mutations in exon 11

could produce a partial BRCA1 protein encoded by the known exon 11 splice variant, while the full-length protein is lost by the process of NMD.[6] Murine embryos carrying the exon 11–deleted isoform survive longer than those that are *BRCA1* null, and *BRCA1* that has lost exon 11 appear to retain partial function.[31] Thus, for *BRCA1*, it is biologically plausible that individuals carrying mutations within exon 11 (and the OCCR) may have a different phenotype than other mutations. In *BRCA2*, we have identified OCCRs, coincident with the 8 BRC repeats. Mutations in this region appear to be associated with NMD, which would lead to loss of *BRCA2* expression.[7] However, it is possible that there is persistence of an alternatively spliced variant of *BRCA2*, without exon 11 (as for *BRCA1*), which would represent in-frame mutations. In addition, the *BRCA2* BRC repeats interact with *RAD51*, which has been consistently shown to be a modifier of *BRCA2*-associated breast and ovarian cancer risk.[32] Without the BRC repeats, *BRCA2* might differ in interactions with *RAD51* and lead to genotype-phenotype variation. However, the biological basis of the *BRCA2* OCCR remains speculative, in particular as it does not extend throughout all of exon 11.

In *BRCA2*, several putative BCCRs were defined. The 3′ BCCR coincides approximately with mutations occurring in the oligonucleotide binding (OB) fold domains and the tower domain. When examined independently, both of these domains were associated with relatively elevated breast cancer risk and lower ovarian cancer risk. These mutations in *BRCA2* would be predicted to undergo NMD. However, it has been demonstrated experimentally for only a few mutations, leaving the functional basis unknown.[7]

We have also identified a decreased risk of ovarian cancer associated with all types of mutations predicted not to lead to NMD in *BRCA2*; the estimated risk was only significant for all mutations together and those mutations leading to in-frame splice site or frame shift mutations. These mutations all occur after nucleotide 7000 in the C-terminus of *BRCA2*, which includes the DNA binding domains, tower domains, and OB folds.[33] These functional domains are associated with localization of *BRCA2* to sites of double-stranded DNA breaks to accomplish repair.[33] These data suggest that intact protein may be protective when it comes to ovarian cancer risk. However, the number of individuals is small and further replication is needed.

A number of limitations of this research may influence the generalizability and translational potential of this research. Despite the very large sample size, we were not able to investigate some mutation and risk groups with adequate statistical power. Carriers of *BRCA2* mutations composed a smaller sample set; in particular, the number of women with *BRCA2*-associated ovarian cancers was relatively small. Although all women with a documented disease-associated mutation in the CIMBA database were included, some populations use screening for founder mutations as a primary method of mutation detection, such as for the 3 Ashkenazi Jewish mutations. This testing strategy may lead to underreporting of nonfounder mutations. As such, some bias in the ascertainment of the full spectrum of mutations could have occurred. The ascertainment strategy generally followed clinical and research protocols similar across all centers. However, we did not correct for ascertainment, and thus bias may have affected some variables (eg, age at diagnosis), which should be interpreted with caution. Mutation testing was performed using methods acceptable for clinical practice at each center, which was not uniform across all centers.

The present sample set does not reflect the general population of all mutation carriers but reflects those women who have undergone genetic testing for *BRCA1/2* mutations, a relevant population of inference. We have presented the mutations in terms of category or effect, but these designations are in some cases extrapolated based on experimental evidence for similar mutations. An example is the designation of NMD inferred from mutation location, which is based on experimental validation of only a small proportion of the mutations.[6,7] Similarly, inference of protein truncation based on predicted protein-truncating mutations without experimental verification may lead to erroneous classification.[25] Penetrances that are presented here are limited because other factors that are not accounted for here could influence these estimates. These factors include family history and competing mortality. These risks also depend on knowing the true prevalence of the mutation-specific classes, which is likely to be population-specific.

In addition, the present report of more than 32 000 mutation carriers could include some of those individuals who were included in the 1995 and 1997 articles that originally reported the OCCR.[3] It is not possible at this time to know if any of the 32 families carrying *BRCA1* mutations or 25 families carrying *BRCA2* originally reported also are included in the present sample. However, it is highly unlikely that the small sample of individuals represented in the original reports would outweigh a potential null effect among the more than 32 000 individuals studied here.

This study is the first step in defining differences in risk associated with location and type of *BRCA1* and *BRCA2* mutations. Pending additional mechanistic insights into the observed associations, knowledge of mutation-specific risks could provide important information for clinical risk assessment among *BRCA1/2* mutation carriers, but further systematic studies will be required to determine the absolute cancer risks associated with different mutations. It is yet to be determined what level of absolute risk change will influence decision making among carriers of *BRCA1/2* mutations. Additional research will be required to better understand what level of risk difference will change decision making and standards of care, such as preventive surgery,[34] for carriers of *BRCA1* and *BRCA2* mutations.

Conclusions

Breast and ovarian cancer risks varied by type and location of *BRCA1/2* mutations. With appropriate validation, these data may have implications for risk assessment and cancer prevention decision making among carriers of *BRCA1* and *BRCA2* mutations.

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